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Markers of Chronic Obstructive Pulmonary Disease are associated with mortality in people living with HIV

Running head: COPD and mortality in HIV

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Abstract

Objective. Aging people living with HIV (PLWH) face an increased burden of comorbidities, including chronic obstructive pulmonary disease (COPD). The impact of COPD on mortality in HIV remains unclear. We examined associations between markers of COPD and mortality among PLWH and uninfected subjects.

Design. Longitudinal analysis of the Examinations of HIV-Associated Lung Emphysema (EXHALE) cohort study.

Methods. EXHALE includes 196 PLWH and 165 uninfected smoking-matched subjects who underwent pulmonary function testing and CT scans to define COPD and were followed. We determined associations between markers of COPD with mortality using multivariable Cox regression models, adjusted for smoking and the VACS Index, a validated predictor of mortality in HIV.

Results. Median follow-up time was 6.9 years; the mortality rate was 2.7 per 100-person-years among PLWH and 1.7 per 100-person-years among uninfected subjects ($p=0.11$). The VACS Index was associated with mortality in both PLWH and uninfected subjects. In multivariable models, pulmonary function and CT characteristics defining COPD were associated with mortality in PLWH: those with airflow obstruction ($FEV_1/FVC < 0.7$) had 3.1 times the risk of death (HR 3.1 [95% CI 1.4-7.1]), compared to those without; those with emphysema (>10% burden) had 2.4 times the risk of death (HR 2.4 [95% CI 1.1-5.5]) compared to those with $\leq 10\%$ emphysema. In uninfected subjects, pulmonary variables were not significantly associated with mortality, which may reflect fewer deaths limiting power.

Conclusions. Markers of COPD were associated with greater mortality in PLWH, independent of the VACS Index. COPD is likely an important contributor to mortality in contemporary PLWH.

Introduction

In the contemporary antiretroviral therapy (ART) era, people living with HIV (PLWH) are surviving to older age; [1] however, these patients face an increased burden of comorbidities. [2-4] The impact of this multimorbidity is profound; PLWH experience excess mortality compared to uninfected persons, [5, 6] and most of these deaths are attributable to chronic non-AIDS-related disease. [7-9] The prevalence of chronic obstructive pulmonary disease (COPD), and the emphysema subtype, is greater in PLWH as well. [10-15] This is largely due to more smoking in PLWH, but there may be an independent contribution related to HIV infection. [16-19]

COPD is associated with increased symptoms, hospitalization and frailty in PLWH, [20-23] but an association with mortality has not been determined. Understanding the impact of COPD on mortality in HIV is important in considering the public health impact and clinical significance of COPD in this population and to support smoking cessation interventions and early COPD diagnosis and management. Specific COPD markers may also be useful in prediction models for mortality in HIV. In this study, we sought to determine whether physiologic and radiographic markers of COPD were associated with mortality in a cohort of PLWH and uninfected subjects. Moreover, we sought to determine whether these markers of COPD were independent of the Veterans Aging Cohort Study (VACS) Index (<https://medicine.yale.edu/intmed/vacs/>), a validated research and clinical tool that predicts mortality in PLWH but does not include markers of pulmonary dysfunction. [24]

Methods

This study utilizes the Examinations of HIV-Associated Lung Emphysema (EXHALE) Study, a pulmonary substudy of VACS described in detail elsewhere. [25, 26] VACS subjects were enrolled into EXHALE at 4 Veterans Affairs (VA) Medical Centers (VAMCs) between 2009-2012. PLWH and uninfected subjects were recruited matched on smoking status. Subjects were ineligible if they had chronic pulmonary diseases other than COPD or asthma, and had experienced recent acute respiratory symptoms. Subjects were followed from enrollment

through March 2017, with deaths determined from the VA vital status file. Cause of death information, summarized from ICD-9 and ICD-10 coding, was available through December 2014. 366 patients were enrolled and underwent any testing, with 5 patients excluded due to abnormalities precluding further testing (4 with aortic aneurysms and 1 with a pulmonary mass). 342 subjects were included in pulmonary function testing (PFTs) analyses and 323 included in chest CT analyses, based on completion of tests.

Demographic and smoking information was collected from self-completed surveys at enrollment. Laboratory data was obtained via electronic medical record (EMR). The VACS Index was calculated at enrollment using EMR data closest to EXHALE enrollment, no longer than 12 months prior. The VACS Index was developed in Veterans and externally validated, and predicts mortality in PLWH and uninfected persons. [24, 27-29] The VACS Index incorporates age, CD4, viral load, hepatitis C serostatus, hemoglobin, glomerular filtration rate (eGFR) and the Fibrosis-4 Index (FIB-4) for liver fibrosis. The Index assumes normal CD4 count and no detectable viral load for uninfected subjects.

Pulmonary data obtained included PFTs and chest CT images. PFTs were performed to American Thoracic Society (ATS) standards at clinical laboratories. Testing included post-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and diffusion capacity (DLCO). Percent-predicted values were calculated based on National Health and Nutrition Examination Survey (NHANES) III data. [30-34] COPD was defined as airflow obstruction ($FEV1/FVC < 0.7$), [35] and alternatively as FEV1/FVC below lower limit of normal (LLN, $< 5^{\text{th}}$ percentile). [30] CT scans were performed at baseline using a protocol described in detail previously. [25] These scans were interpreted by a thoracic radiologist blinded to clinical data to determine semi-quantitative emphysema scoring, which was dichotomized at the overall median of $>$ or $\leq 10\%$ involvement. Scans also underwent quantitative emphysema analysis using University of Pittsburgh software for lung segmentation followed by density mask

technique to quantify percentage of low attenuation areas (Hounsfield units \leq -950, %LAA) consistent with emphysema. [36-39]

Baseline characteristics were compared by HIV status using Chi-squared testing. We used Cox proportional hazards regression to examine variable associations with mortality, stratified by HIV status. Patients were right-censored at end of follow-up (March 2017) or death. There was no loss-to-follow-up for the death outcome. Separate bivariate Cox models were created for variables including the pulmonary variables: airflow obstruction (by both methods), FEV1 %-predicted, FVC %-predicted, DLCO %-predicted, >10% emphysema, %LAA. Seven multivariable models for PLWH and uninfected subjects were created for the pulmonary variables adjusted for smoking pack-years and the VACS Index. We created 3 models including the entire cohort with multiplicative interaction terms between HIV status and airflow obstruction and emphysema >10%, respectively. In the models, sex was not included as there were no deaths among the 20 women, and race/ethnicity was not included and was not associated with the variables of interest or outcome. All models had limited power to detect even moderate associations with mortality: We had 80% power to detect a mortality HR of 2.2 for categorical variables of interest in the entire cohort and 80% power to detect a mortality HR of 2.7 (in PLWH) and 3.7 (in uninfected subjects) for categorical variables of interest in stratified models.

Results

Of 361 subjects, 196 were PLWH and 165 were uninfected (Table 1). Median enrollment age was 54 (interquartile range [IQR] 50-59) and 94% were male. PLWH largely had well-controlled disease: 14% had CD4 count <200 cells/ μ L and 17% had viral load >400 copies/mL. The median VACS Index was 29 (IQR 18-42) in PLWH compared to 18 (IQR 12-27) in the uninfected (p <0.001). There was a trend towards higher pack years of smoking in PLWH. PLWH had lower DLCO %-predicted (53 vs. 57, p =0.005), and higher prevalence of emphysema >10% (31% vs. 16%, p =0.003). Median follow-up was 6.9 years and similar by HIV status. The majority (93%) of subjects alive at study end had VA follow-up within the last 12 months. The

mortality rate was 2.7 per 100-person-years among PLWH (33 deaths) and 1.7 per 100-person-years among uninfected subjects (18 deaths) ($p=0.11$). Of those with available cause of death data (59%), 23% died from heart disease, 37% from cancer and 6.7% directly from respiratory causes. Only 9.5% of PLWH died from causes related to HIV/AIDS. The VACS Index was associated with mortality in both PLWH and the uninfected, as was older age and other specific VACS Index components. (Supplemental Table 1).

The pulmonary markers were associated with mortality in unadjusted and adjusted models (Supplemental Figure 1, Table 2). In adjusted models, airflow obstruction ($FEV1/FVC < 0.7$: HR 3.1, 95% CI 1.4-7.1, $FEV1/FVC < LLN$: HR 4.3, 95% CI 1.9-9.8), $FEV1$ %-predicted (HR 1.3, 95% CI 1.0-1.7, 10-unit decrease), $DLCO$ %-predicted (HR 1.8, 95% CI 1.3-2.5, 10-unit decrease) and emphysema as semi-quantitative $>10\%$ (HR 2.4, 95% CI 1.1-5.5) and %LAA (HR 1.3, 95% CI 1.1-1.7, 5% increase) were associated with mortality in PLWH, independent of smoking pack-years and the VACS Index. Among the uninfected, there were no significant associations with mortality in adjusted models, though emphysema $>10\%$ had a similar hazard ratio (HR 2.1, 95% CI 0.62-7.4). In inclusive models for the whole cohort, interaction between HIV status and airflow obstruction was significantly associated with mortality, using either definition of obstruction ($p=0.04$ for both). There was no significant interaction between emphysema $>10\%$ and HIV status.

Discussion

In this study, we examined the association of COPD with mortality in a longitudinal cohort of PLWH and uninfected subjects. We found that markers that define COPD (airflow obstruction), grade severity ($FEV1$) and emphysema (emphysema $>10\%$, %LAA and $DLCO$) were associated with mortality in PLWH, independent of smoking and the VACS Index.

COPD is the third leading cause of death in the United States and outpacing other leading causes of mortality. [40] The impact of COPD is also underestimated, as concomitant COPD is an unreported contributor to other causes of death, and under-diagnosed. [40-43] In

the general population, FEV1 decline, the key measure grading COPD severity, is a well-established predictor of death in patients with COPD. [44-46] To our knowledge, the association of markers of COPD with mortality in HIV has not been previously established. Previous studies suggest that COPD is not only more prevalent in PLWH, but also has substantial clinical impact. COPD may be associated with a higher symptom burden in PLWH, [22, 23, 47] and PLWH are more likely to have acute exacerbations and hospitalizations related to COPD. [48, 49] Those who are admitted with COPD-related diagnoses may face higher in-hospital mortality. [50] PLWH may also experience an accelerated decline in pulmonary function. [51-53] We have previously shown that emphysema is associated with increased immune activation and inflammation, [25, 54] and increased functional limitation in PLWH. [26]

Our study adds to this literature by establishing that multiple markers of COPD and the emphysema subtype are associated with increased mortality among PLWH. While the majority of cohort deaths were not directly related to respiratory causes, as above, COPD is an important contributor or co-factor in other causes of death from chronic disease. [43] Given the prevalence and impact of COPD in HIV, these findings support increased attention to smoking cessation in PLWH to reduce COPD incidence and attenuate pulmonary function decline, and there are limited studies addressing cessation interventions in PLWH. [55, 56] Our findings also highlight the importance of interventions to diagnose and manage COPD in PLWH to prevent decline in health. Finally, markers of COPD may have a role in mortality prediction models in HIV, such as the VACS Index, though this will require further study. Our finding of no significant associations with mortality among uninfected subjects is reflective of limited power, and should not imply that COPD is not associated with mortality in the general population. However, the finding of significant interaction between airflow obstruction and HIV status (whether defined as a fixed ratio or LLN) is intriguing, suggesting a potential differential impact of COPD on mortality in PLWH.

This study has several strengths. First, detailed smoking information on subjects allowed us to understand the contribution of COPD markers independent of smoking. Second, we carefully characterized physiologic and radiographic pulmonary data, including CT images that were analyzed by semi-quantitative and quantitative methods to define emphysema. Finally, we had comprehensive follow-up on enrolled participants, with a median of 6.9 years of follow-up. Our study had certain weaknesses as well. Participants were largely male Veterans, which may limit generalizability. We also did not have comprehensive information on cause of death. Finally, the study power limited our ability to detect associations with mortality, particularly in uninfected subjects.

In conclusion, we found that markers of COPD and emphysema were associated with mortality in PLWH. These findings underscore the importance of COPD in aging PLWH, and the need for attention to smoking cessation, COPD diagnosis and COPD management in patients with HIV. We plan further study to examine these markers in a larger cohort of PLWH, adjust for other comorbidities such as cardiovascular disease that often co-exist with COPD, and determine whether pulmonary markers add predictive value to the VACS Index.

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Tables

Table 1. Baseline characteristics by HIV status (n=361)

| Characteristic | Total Cohort (n=361) | PLWH (n=196) | HIV-uninfected (n=165) | P-value (PLWH vs. uninfected) |
|---|---------------------------------|-------------------------|-----------------------------------|--|
| Age (years) | 54 (50-59) | 55 (51-60) | 53 (49-53) | 0.08 |
| Male (%) | 94 | 98 | 89 | <0.001 |
| Race/ethnicity | | | | 0.20 |
| Black (%) | 68 | 71 | 64 | |
| White (%) | 17 | 13 | 21 | |
| Hispanic (%) | 12 | 12 | 13 | |
| Other (%) | 3.1 | 3.6 | 2.4 | |
| BMI | 28 (24-32) | 26 (24-30) | 30 (26-34) | <0.001 |
| Smoking status | | | | 0.57 |
| Current (%) | 61 | 64 | 58 | |
| Former (%) | 22 | 21 | 24 | |
| Never (%) | 17 | 15 | 18 | |
| Pack-years of smoking (Current or former smokers) | 24 (11-40) | 26 (13-42) | 20 (7.9-37) | 0.06 |
| HCV Infection (%) | 30 | 37 | 21 | <0.001 |
| Reported IDU ever (%) | 26 | 32 | 18 | 0.002 |
| CD4 cell count, cells/ μ L (median) | | 441 (298- 618) | | |
| CD4 cell count <200 cells/ μ L (%) | | 14 | | |
| Viral load, copies/mL (median) | | 48 (48-103) | | |
| Viral load >400 copies/mL (%) | | 17 | | |
| History of PCP (%) | | 2.0 | | |
| History of TB (%) | | 3.9 | | |
| VACS Index | 23 (12-34) | 29 (18-42) | 18 (12-27) | <0.001 |
| FEV1 %-predicted | 91 (79-104) | 92 (81-106) | 91 (78-101) | 0.32 |
| FVC %-predicted | 95 (85-104) | 96 (86-106) | 92 (84-103) | 0.09 |
| Airflow obstruction (FEV1/FVC<0.7) (%) | 20 | 20 | 20 | 0.94 |
| Airflow obstruction | 16 | 17 | 15 | 0.61 |

| | | | | |
|---|---------------|---------------|---------------|-------|
| (FEV1/FVC<LLN) % | | | | |
| DLCO %-predicted | 55 (46-68) | 53 (43-65) | 57 (48-71) | 0.005 |
| Emphysema >10% involvement (%) | 24 | 31 | 16 | 0.003 |
| Fraction HU ≤-950 (LAA) | 1.9 (0.6-4.8) | 2.1 (0.7-5.1) | 1.7 (0.5-4.5) | 0.12 |
| Follow-up time, months | 84 (64-92) | 85 (61-92) | 84 (68-90) | 0.71 |
| Died in follow-up (n, %) | 51 (14%) | 33 (17%) | 18 (11%) | 0.11 |
| Cause of death (n, %) ^a | | | | |
| Unavailable | 21 | 12 | 9 | |
| Heart disease | 7 (23%) | 2 (9.5%) | 5 (56%) | |
| Cancer | 11 (37%) | 11 (52%) | 0 | |
| Respiratory | 2 (6.7%) | 2 (9.5%) | 0 | |
| HIV related | 2 (6.7%) | 2 (9.5%) | 0 | |
| Other infections | 5 (17%) | 2 (9.5%) | 3 (33%) | |
| Other | 3 (10%) | 2 (9.5%) | 1 (11%) | |
| VAMC follow-up in living subjects in last 12 months (%) | 93 | 93 | 93 | 0.80 |

^aCause of death information only available through 12/31/14. Deaths after this date listed as unavailable. Percentage reflects percent of known causes of death.

Characteristics presented as median (with intraquartile range), n or %, where appropriate.

PLWH=persons living with HIV, BMI = body mass index, HCV=hepatitis C virus, IDU= injection drug use, PCP=*Pneumocystis pneumonia*, TB= tuberculosis VACS = Veterans Aging Cohort Study, FEV1 = forced expiratory volume 1-second, FVC = forced vital capacity, LLN= lower limit of normal, DLCO = diffusion capacity, HU= Hounsfield units, LAA=low attenuation areas

Table 2. Hazard ratios for mortality for pulmonary function and chest CT variables in PLWH and uninfected subjects (n=361)

| Variable | PLWH (n=196 with 33 deaths) | | | HIV-uninfected (n=165 with 18 deaths) | | |
|--|-----------------------------|--|--|---------------------------------------|--|--|
| | Unadjusted HR | HR adjusted for VACS Index ^a | HR adjusted for VACS Index and smoking ^b | Unadjusted HR | HR adjusted for VACS Index ^a | HR adjusted for VACS Index and smoking ^b |
| Airflow obstruction (FEV1/FVC<0.7) | 3.2 (1.5-6.5) | 2.9 (1.4-6.1) | 3.1 (1.4-7.1) | 1.2 (0.37-3.6) | 0.77 (0.24-2.4) | 0.65 (0.19-2.2) |
| Airflow obstruction (FEV1/FVC<LLN) | 4.1 (2.0-8.4) | 3.8 (1.8-8.1) | 4.3 (1.9-9.8) | 1.2 (0.33-4.2) | 1.1 (0.30-3.8) | 0.91 (0.25-3.2) |
| Lower FEV1 %- predicted^c | 1.4 (1.1-1.7) | 1.4 (1.1-1.8) | 1.3 (1.0-1.7) | 1.1 (0.81-1.4) | 0.97 (0.73-1.3) | 0.92 (0.68-1.3) |
| Lower FVC %- predicted^c | 1.1 (0.90- 1.4) | 1.1 (0.84-1.4) | 0.93 (0.71-1.2) | 1.1 (0.81-1.5) | 1.0 (0.75-1.3) | 0.97 (0.71-1.3) |
| Lower DLCO %- predicted^c | 1.8 (1.4-2.4) | 1.7 (1.3-2.3) | 1.8 (1.3-2.5) | 1.6 (1.1-2.4) | 1.2 (0.84-1.8) | 1.2 (0.80-1.7) |
| Emphysema >10% involvement | 2.0 (1.0-4.1) | 2.3 (1.1-4.9) | 2.4 (1.1-5.5) | 2.7 (0.92-7.8) | 2.1 (0.69-6.1) | 2.1 (0.62-7.4) |
| Higher %LAA on CT^d | 1.3 (1.1-1.6) | 1.3 (1.1-1.6) | 1.3 (1.1-1.7) | 1.0 (0.62-1.8) | 1.0 (0.59-1.7) | 1.0 (0.59-1.7) |

PLWH= persons living with HIV; FEV1 = forced expiratory volume in 1 second (post-bronchodilator); FVC = forced vital capacity

(post-bronchodilator); LLN=lower limit of normal; DLCO = diffusion capacity (corrected for hemoglobin); LAA = low attenuation areas

^a adjusted for the VACS Index (which incorporates age, CD4 cell count, HIV viral load, hepatitis C serostatus, hemoglobin, glomerular filtration rate (eGFR) and the Fibrosis-4 Index (Fib-4) for liver fibrosis)

^b adjusted for the VACS Index and pack-years of smoking

^c HR per 10-unit decrease

^d HR per 5% increase

