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Emphysema and soluble CD14 are associated with pulmonary nodules in HIV-infected patients: Implications for lung cancer screening

Matthew TRIPLETTE¹, Keith M. SIGEL², Alison MORRIS³, Shahida SHAHRIR¹, Juan P. WISNIVESKY², Chung Y. KONG⁴, Phillip T. DIAZ⁵, Alycia PETRAGLIA³, and Kristina CROTHERS¹

¹Department of Medicine, University of Washington, Seattle, WA

²Department of Medicine, Icahn School of Medicine at Mt. Sinai, New York, NY

³Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

⁴Department of Radiology, Massachusetts General Hospital, Boston, MA

⁵Department of Medicine, Ohio State University, Columbus, OH

Abstract

Objective—Lung cancer screening may benefit HIV-infected (HIV+) smokers due to an elevated risk of lung cancer, but may have unique harms because of HIV-specific risk factors for false-positive screens. This study seeks to understand whether inflammatory biomarkers and markers of chronic lung disease are associated with non-calcified nodules ≥4mm in HIV-infected (HIV+) compared to uninfected patients.

Design—This is a cohort study of the Examinations of HIV-Associated Lung Emphysema (EXHALE), including 158 HIV+ and 133 HIV-uninfected participants.

Methods—Participants underwent a laboratory assessment (including measurement of D-dimer, IL-6 and soluble CD14), chest CT and pulmonary function testing. We created multivariable logistic regression models to determine predictors of non-calcified nodules in the participants stratified by HIV status, with attention to semi-qualitative scoring of radiographic emphysema, markers of pulmonary function and inflammatory biomarkers.

Results—Of the 291 participants, 69 had non-calcified nodules ≥4mm on chest CT. As previously reported, there was no difference in prevalence of these nodules by HIV status. Emphysema >10% and elevated soluble CD14 demonstrated an association with non-calcified nodules in HIV+ participants independent of smoking status, CD4 cell count, HIV viral load, and pulmonary function.

Conclusions—Emphysema and soluble CD14, a marker of immune activation, was associated with a higher prevalence of non-calcified nodules on chest CT in HIV+ participants. Patients with

Corresponding Author: Matthew Triplette, 325 9th Avenue, Campus Box 359762, Seattle, Washington 98104. mtrip@uw.edu.

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chronic immune activation and emphysema may be at higher risk for both false-positive findings and incident lung cancer, thus screening in this group requires further study to understand the balance of benefits and harms.

MeSH Key words

HIV; Chronic Obstruction Pulmonary Disease; Pulmonary Nodule; Emphysema; Early Detection of Cancer; Lung Cancer

Introduction

HIV-infected (HIV+) patients have increased risk of lung cancer, [2–4] secondary to smoking behavior, [5] and HIV-associated inflammatory mechanisms. [6–8] Lung cancer screening is now recommended for patients ages 55–77 with a 30 pack-year smoking history using annual low dose chest CT (LDCT) based on the National Lung Screening Trial (NLST), which demonstrated a 20% lung cancer mortality benefit. [9–12] This trial revealed that 1 in 4 patients undergoing initial screen have positive findings (most often nodules), and that >96% of positive screens do not represent lung cancer. [10] These nodules are usually infection/inflammatory sequelae (i.e. granulomas) or hamartomas, but can result from several other causes. [13] At the time of detection, it is not known if these nodules are false-positives and they often require diagnostic procedures with associated morbidity and mortality and additional scans. [10] An understanding of risk factors for nodules is required to inform overall screening benefits and harms.

The optimal approach to lung cancer screening in HIV+ smokers remains uncertain. [14, 15] HIV+ smokers have a high burden of lung cancer; however, the higher incidence of infections, inflammation and chronic lung disease may lead to false-positives. In our prior study, we found a similar prevalence of nodules in HIV+ and uninfected participants, but higher prevalence in HIV+ patients with CD4<200 cells/ μ L. [16] To further inform benefits and harms of screening in HIV+ patients, we examined the relationship between markers of chronic lung disease and inflammation with significant CT-detected nodules, examining pulmonary function, radiographic emphysema and systemic biomarkers of inflammation (IL-6), altered coagulation (D-dimer) and immune activation (soluble-CD14 [sCD14]) previously associated with pulmonary and other end-organ disease in HIV+ patients. [17–21]

Methods

This study is a secondary cross-sectional analysis of Examinations of HIV-Associated Lung Emphysema (EXHALE), a Veterans Aging Cohort Study (VACS) substudy. The study design is described in greater detail elsewhere. [22–24] A total of 366 HIV+ and uninfected VACS participants, block-matched on current smoking status, were recruited at 4 Veterans Affairs (VA) Medical Centers (VAMCs) between 2009–2012. The analytic cohort includes 291 participants (158 HIV+ and 133 uninfected) who were not excluded as screen failures (n=6), completed baseline CT assessment and pulmonary function testing (PFTs). Participants provided written consent and site institutional review boards approved the study protocol.

Participants underwent a baseline chest CT with a standardized protocol, described elsewhere. [16, 23] Scans underwent a clinical read by an onsite radiologist, abstracted by a study investigator blinded to patient information to determine nodule presence and characteristics. Nodules were considered positive if they were ≥ 4 mm and non-calcified (hereafter referred to as NCN), per NLST criteria. [10] A thoracic radiologist performed a blinded research interpretation of CTs for semi-quantitative emphysema scoring. Emphysema severity was scored 0 (no emphysema) through 5 ($>75\%$ emphysema) as described in prior studies, and dichotomized for main analyses at 2 ($>10\%$ or $\geq 10\%$), the median score overall. [22–24]

Participants underwent PFTs including post-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and diffusion capacity (DLCO). Values were standardized to %-predicted values for age, sex, height and race (and hemoglobin for DLCO) using National Health and Nutrition Examination Survey (NHANES) III data. [25–29] Airflow obstruction was defined as FEV1/FVC <0.7 . Demographic and laboratory data were collected from the electronic health record. sCD14 (in ng/mL), D-dimer (in $\mu\text{g/mL}$) and IL-6 (in pg/mL) were measured at enrollment (Laboratory for Clinical Biochemistry Research, University of Vermont). Participants completed standardized questionnaires including a detailed smoking assessment.

Baseline characteristics were reported for the cohort, and stratified by HIV status and presence of NCN using χ^2 testing or Wilcoxon ranksum testing. We determined independent associations of markers of chronic lung disease and biomarkers with NCN using multivariable logistic regression. The entire cohort model incorporated emphysema $>10\%$, %-predicted FEV1, %-predicted DLCO, biomarkers (quartiles of sCD14 as neither IL-6 nor D-dimer demonstrated association with the outcome in bivariate analyses) with adjustment for HIV status, age, sex, race and smoking pack-years. We created similar models stratified by HIV, with the model for HIV+ participants incorporating CD4 count and HIV viral load. We also tested the trend of association between emphysema categories and NCN using Cuzick's non-parametric test. Analyses were performed using STATA 14.0 (StataCorp LP, College Station, TX). Results were considered significant at two-sided p-value <0.05 .

Results

Of the 291 participants, 158 (54%) were HIV+. The median age was 53 (Interquartile Range [IQR] 48–58) years old, and most (94%) were male (Table 1). 69% of participants were black, and 12% reported Hispanic ethnicity. Most participants were either current (62%) or former (21%) smokers. Sixty-nine (24%) participants had ≥ 1 NCN on baseline CT scan.

HIV+ participants were slightly older, with lower body mass index (BMI), and reported greater pneumonia history; 14% had a CD4 count <200 cells/ μL and 33% had a viral load >50 copies/mL. There were similar rates of current smoking by HIV status as participants were matched on this variable, though HIV+ smoked more pack-years (Table E1). HIV+ participants were more likely to have $>10\%$ emphysema (33% vs. 16%, $p=0.001$) and lower DLCO. There was a similar prevalence of NCN in the HIV+ (25%) and the uninfected (22%) participants ($p=0.48$).

There were notable differences in participants with and without NCN (Table 1). Emphysema >10% was present in 39% of participants with NCN, compared to 21% of participants without ($p=0.003$). NCN were also more likely with greater emphysema severity ($p=0.001$) (Figure E1). Those with NCN were more likely to have airflow obstruction (31% vs. 19%, $p=0.03$) and had a lower median DLCO %-predicted (49 vs. 54, $p=0.02$). Among biomarkers, those with NCN had higher median sCD14 (1674 ng/mL vs. 1492 ng/mL, $p=0.006$); IL-6 and D-dimer were not associated with NCN. HIV-related clinical markers were associated with NCN in HIV+ participants: CD4 count was <200 cells/ μ L in 28% of those with NCN compared to 9.4% of those without NCN ($p=0.003$), and viral load was >50 copies/mL in 49% of those with NCN compared to 27% of those without NCN ($p=0.002$).

There were differences in the association of markers of chronic lung disease and biomarkers with NCN by HIV status. Among HIV+ participants, emphysema >10% was more common among those with NCN (49% vs. 27%, $p=0.02$), as was airflow obstruction (34% vs. 18%, $p=0.03$) and lower median DLCO %-predicted (48 vs. 54, $p=0.03$). Among the uninfected, there was a non-significant trend towards association of emphysema ($p=0.15$) with NCN, but neither PFTs, nor biomarkers, were associated with NCN.

In overall models, emphysema >10% was associated with an increased risk (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.1–4.9) of NCN. In models stratified by HIV status, among the HIV+ participants, emphysema >10% was associated with increased risk (OR 2.7, 95% CI 1.0–7.5) of NCN and each progressive quartile of sCD14 was associated with an increased risk (OR 1.9, 95% CI 1.2–2.9) of NCN (Table 2). Smoking, CD4 count and viral load were not independently associated with NCN in multivariable models. Among the uninfected participants, there were no significant associations with NCN.

Discussion

In this study, we examined associations between markers that reflect chronic lung disease and systemic inflammation with incidental pulmonary NCN, and determined differences by HIV status. In our previous study, we found participants with and without HIV had similar prevalence of NCN, although low CD4 count was associated with NCN in HIV+ participants; few of these NCN were later diagnosed as lung cancer ($n=3$; 1 other lung cancer case in follow-up), with the majority being non-specific benign nodules. [16] We extend this work and demonstrate that >10% emphysema and higher systemic levels of sCD14 are independently associated with NCN in HIV+ participants.

NCNs were most strongly associated with emphysema. Emphysema, characterized by destruction of normal pulmonary architecture may lead to areas of heterogeneity and hyper-density interpreted as NCN. Emphysema is also associated with increased pulmonary infections, [36, 37] which may lead to non-calcified granulomas. Moreover, emphysema has been associated with pulmonary and systemic inflammation, [38, 39] which may lead to inflammatory nodules. Emphysema may be particularly important in HIV—the burden is greater, [40] and emphysema may reflect HIV-related inflammation and immune activation. [24, 41]

sCD14 was associated with NCN in HIV+ participants, and there were no other biomarker associations, suggesting a potential relationship between immune activation and NCN. sCD14 is a monocyte activation product, functioning as a co-receptor for lipopolysaccharide (LPS). It reflects increased gut microbial translocation in HIV, [20, 42–44] and this may be connected to pulmonary inflammation (referred to as the gut-lung axis).[45–47] More likely it is related to nodules through non-specific mechanisms—it is a marker of immune activation, its secretion is stimulated in response to other inflammatory cytokines, [48] and has been used as a marker of inflammatory response in HIV. [20, 49–52] In this study, sCD14 was associated with NCN in the HIV+ participants only; this differential association will require further exploration.

Although all study participants do not meet standard criteria for lung cancer screening, these findings have implications for screening as incidental findings will increase with widespread screening implementation. A multicenter study of implementation revealed that among high-risk Veterans, significant nodules were present in 56% but only 1.5% were diagnosed as lung cancer in follow-up. [30] Understanding risk factors for both lung cancer and incidental nodules are needed to optimize the benefits and harms of screening. Our results indicate that both immune activation and emphysema may be risk factors for CT-detected NCN in those with HIV. There may also be a greater incidence of lung cancer in these patients, [33–35] so how these factors affect overall screening in HIV+ patients will require further study.

This study has certain limitations. The participants are Veterans and largely male, limiting generalizability, though they were racially, ethnically and geographically diverse. The CT assessments for emphysema, while blinded, were based on a single radiologic read. We were limited by power, which may have resulted in non-significant associations among the uninfected participants. Weaker study associations (such as the relationship with NCN and sCD14) should be interpreted cautiously given the possibility of residual confounding. Finally, there are other algorithms to define significant nodules and we used a sensitive size threshold based on the NLST.

In conclusion, in a cohort of HIV+ and uninfected asymptomatic outpatients we demonstrated that among HIV+ participants, radiographic emphysema >10% and elevated systemic levels of sCD14, a marker of monocyte activation, were associated with NCN independent of pulmonary function, smoking and HIV markers. These findings have important implications for lung cancer screening in patients with HIV: While patients with HIV may be at higher risk for lung cancer, there may be certain groups, including those with radiographic emphysema and potentially chronic immune activation, who are also at higher risk of false-positive findings. Future studies are needed to better understand the potential harms and benefits of lung cancer screening in HIV+ patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Baseline characteristics by presence or absence of non-calcified nodules ≥ 4 mm in total cohort¹ (n=291)

Characteristic	NCN ≥ 4 mm (n=69)	No NCN ≥ 4 mm (n=222)	p-value
HIV-infected, %	58%	53%	0.48
Age, years	55 (50–58)	53 (47–58)	0.19
Male, %	94	94	0.88
Race/Ethnicity			0.50
White, %	16	15	
Black, %	74	67	
Hispanic, %	8.7	14	
Other, %	1.5	4.0	
BMI	26 (24–29)	28 (25–32)	0.005
History of pneumonia, %	25	25	0.92
Smoking status			0.03
Current smokers, %	74	59	
Former smokers, %	10	24	
Never smokers, %	16	17	
Pack-years of smoking	21 (8.8–39)	17 (4.0–36)	0.29
Marijuana use (ever), %	78	82	0.51
Injection drug use (ever), %	23	28	0.41
>10% emphysema, %	39	21	0.003
Airflow obstruction (FEV1/FVC<0.7), %	31	19	0.03
FEV1, %-predicted	91 (77–104)	91 (80–102)	0.90
FVC, %-predicted	96 (85–104)	95 (84–103)	0.54
DLCO, %-predicted	49 (42–63)	54 (46–70)	0.02
sCD14 (ng/mL)	1674 (1395–2001)	1492 (1295–1740)	0.006
IL-6 (pg/mL)	1.9 (1.2–3.0)	1.7 (1.1–3.2)	0.68
D-dimer (μ g/mL)	0.31 (0.20–0.47)	0.26 (0.17–0.44)	0.38

¹Data presented as medians (with intraquartile range) or %, where appropriate

FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, DLCO=diffusion capacity, sCD14=soluble CD14, IL-6 = interleukin 6

Table 2

Association between emphysema, pulmonary function and sCD14 with non-calcified nodules ≥4mm (NCN) in models stratified by HIV status

HIV+ participants (n=158)	Unadjusted OR¹	Adjusted OR²
Emphysema >10%	2.5 (1.2–5.4)	2.7 (1.0–7.5)
DLCO %-predicted ³	1.2 (0.96–1.6)	1.1 (0.75–1.6)
FEV1 %-predicted ³	0.95 (0.78–1.2)	0.87 (0.66–1.1)
sCD14⁴	1.7 (1.2–2.5)	1.9 (1.2–2.9)
HIV– participants (n=133)		
Emphysema >10%	2.1 (0.76–6.0)	1.8 (0.52–6.4)
DLCO %-predicted ³	1.2 (0.92–1.5)	1.2 (0.84–1.8)
FEV1 %-predicted ³	1.1 (0.87–1.4)	1.0 (0.75–1.4)
sCD14 ⁴	1.1 (0.69–1.6)	0.85 (0.52–1.4)

¹ Unadjusted OR for simple logistic regression models incorporating term of interest and outcome

² Adjusted OR from single model for HIV+ participants incorporating age, gender, race, pack-years, CD4 cell count and HIV viral level, emphysema >10%, DLCO %-predicted, FEV1 %-predicted and sCD14; and single model for HIV– participants adjusted for above with exception of CD4 cell count and HIV viral level.

³ Odds ratios presented for 10-unit decrease in %-predicted

⁴ Odds ratios for increase in quartile of sCD14