

Title: Diagnostic performance of clinical characteristics to detect airflow limitation in people living with HIV and in uninfected controls

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Objectives: Chronic obstructive pulmonary disease (COPD) is underdiagnosed in the general population and possibly also in people living with HIV (PLWH). We evaluated the diagnostic performance of symptoms and risk factors for assessment of airflow limitation in PLWH and in uninfected controls.

Methods: Spirometry was performed in the Copenhagen Comorbidity in HIV Infection (COCOMO) Study and Copenhagen General Population Study (CGPS) and airflow limitation was defined by forced expiratory volume in one second/forced vital capacity <lower limit of normal. We calculated the sensitivity, specificity, predictive values and area under the curve (AUC) of symptoms and risk factors for assessment of airflow limitation in PLWH and uninfected controls.

Results: A total of 1,083 PLWH and 12,074 uninfected controls were included. The sensitivity for sputum, chronic cough, breathlessness, wheezing, current and cumulative smoking and self-reported COPD was higher, but the specificity lower, in PLWH than in uninfected controls. The negative and positive predictive values were largely similar between the groups. The AUCs were similar or slightly higher in PLWH and highest for >20 pack-years smoked (0.65 (95%CI: 0.58-0.72)) and wheezing (0.64 (95%CI: 0.57-0.71)). A summed score of five variables was associated with slightly higher AUCs in PLWH compared to uninfected controls (0.71 (95% CI: 0.63-0.79) vs. 0.65 (95%CI: 0.63-0.68), $p=0.06$).

Conclusion: Clinical variables were relatively poor discriminators of airflow limitation in PLWH and uninfected controls. Active COPD case finding by screening for symptoms and relevant exposures, as recommended in the general population, is likely to yield similar diagnostic power in PLWH.

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Introduction

Chronic obstructive pulmonary disease (COPD) represents a major global cause of morbidity and mortality (1). Spirometry confirms the presence of chronic airflow limitation and is required to confirm the diagnosis (2). We previously determined the prevalence and risk factors for airflow limitation in people living with HIV (PLWH) and matched uninfected controls from the general population (3). In this study, less than one fifth of PLWH and uninfected controls with airflow limitation reported a previous diagnosis of COPD, suggesting that COPD was underdiagnosed in both groups. Previous studies conducted in the general population have also shown that COPD is universally underdiagnosed (4, 5). Underdiagnoses may represent a missed opportunity to initiate adequate risk factor modifications and therapy.

The optimal approach for COPD case-finding in people living with HIV (PLWH) is unknown, but the European AIDS Clinical Society 2017 Guidelines advocate active case-finding (6), i.e. performing spirometry in individuals with respiratory symptoms and/or relevant exposures such as tobacco smoking, as opposed to routine screening with spirometry. These recommendations are in line with guidelines provided by the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease (GOLD) 2017 Report, the UK National Screening Committee and by the US Preventive Services Task Force (USPSTF) (2, 7, 8).

In this study we evaluated the diagnostic performance of respiratory risk factors and symptoms to detect spirometric airflow limitation in PLWH and uninfected controls.

Methods

Patients and results

The study design has been described elsewhere (3, 9). PLWH and uninfected controls with spirometry from the Copenhagen Comorbidity in HIV Infection (COCOMO) Study and Copenhagen General Population Study (CGPS), respectively, were recruited. Data collection for PLWH was performed at the Department of Infectious Diseases, Rigshospitalet, Copenhagen, and the Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, between March 2015 and November 2016. Matched uninfected controls were recruited between January 2013 and December 2016 at Herlev Hospital, Copenhagen. The study was approved by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350; CGPS: H-KF-01-144/01). Written informed consent was obtained from all participants.

Spirometry

EasyOne ultrasonic spirometer (ndd Medical, Zürich, Switzerland) was used in accordance with American Thoracic Society/European Respiratory Society guidelines. LLN (i.e., equivalent to -1.64 z-score) was calculated for pre-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) using multiethnic prediction equations provided by the Global Lung Function Initiative (10). Airflow limitation was also defined by GOLD stage II disease, i.e., $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted (2).

Data collection

Clinical information was obtained through self-report using identical questionnaires in PLWH and uninfected controls and included information about tobacco exposure and respiratory symptoms. Dyspnea was defined by the modified British Medical Research Council (mMRC) scale ≥ 2 (scale 0-4). Chronic cough, sputum production and wheezing were defined by an affirmative response to the following questions: "Do you have cough lasting > 8 weeks", "Do you have a history of persistent sputum >3 months per year" and "Do you occasionally have whistling or wheezing while breathing?". All individuals also reported whether they had previously been given a diagnosis of COPD by a health care professional.

Statistics

Uninfected controls were frequency matched with PLWH by sex and five age year strata. As previously described, we were able to identify 14 unique uninfected controls per PLWH but for men aged 30-35 it was only possible to identify three controls in each 5-year age interval (3). Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and area under the curve (AUC) were computed for all dichotomized predictors. We also computed the AUC and plotted the receiver operating characteristics (ROC) for the sum of five similar weighted items (i.e. age ≥ 50 years, wheezing, dyspnea, sputum and pack-years of smoking ≥ 20 years), as these were previously included in a questionnaire developed to identify individuals at risk and appropriate for diagnostic evaluation for COPD (11). AUC was computed using the pROC package (v.1.10). As a sensitivity analysis we redefined the criteria for airflow limitation to reflect GOLD stage II disease. Statistical analyses were performed in R (v.3.4.3)(12).

Results

A total of 1,083 PLWH and 12,074 uninfected controls were included. Median [interquartile, IQR] age was 50.1 [42.8-58.0] and 52.1 [45.5-60.9] years, 85.7% and 81.6% were males and 29.2% and 12.9% were current smokers in PLWH and uninfected controls, respectively. In PLWH, median [IQR] CD4 count was 689 cells/mm³ [520-889] and 94.6% has suppression of HIV viral replication. Respiratory symptoms were more common in PLWH. Thus, as previously reported (3), 7.8% vs 4.1% reported dyspnea ($p < 0.0001$), 17.5% vs 9.5% reported sputum production ($p < 0.0001$), 12.9% vs 6.8% reported chronic cough ($p < 0.0001$) and 22.0% vs 15.8% reported wheezing ($p < 0.001$).

Table 1 depicts diagnostic performance of combination of different clinical characteristics (i.e. age ≥ 50 years, wheezing, dyspnea, sputum and cumulative duration of smoking ≥ 20 years). The sensitivity of these variables for detecting FEV₁/FVC < LLN was generally better for PLWH than uninfected controls. Sensitivity was highest for 20 pack-years in both PLWH (56.1%) and (34.7%) in uninfected controls. Conversely, specificities seemed to be poorer in PLWH compared to uninfected controls. PPVs were largely similar between the groups and highest for self-reported COPD in both groups (59.4% and 65.6%, respectively). NPVs were also largely similar and highest

for >20 pack-years smoked for both groups (93.4% and 92.3%, respectively). The discriminative power represented by the AUC tended to be similar or slightly better for PLWH for all binary variables considered and was highest for >20 pack-years of smoking (0.65 (95%CI: 0.58-0.72)).

We also assessed performance of respiratory symptoms in current smokers. Sensitivity of dyspnea, sputum, chronic cough and wheezing was 20.3% vs 12.9%, 43.1% vs 47.8%, 38.6% vs 34.8% and 61.0% vs 52.3% for PLWH and uninfected controls, respectively. Specificity was 89.8% vs 93.2%, 70.7% vs 79.0%, 80.0% vs 84.1%, 59.1% vs 65.0% and AUC was 0.55 vs 0.53 (p=0.50), 0.57 vs 0.63 (p=0.11), 0.59 vs 0.60 (p=0.98) and 0.60 vs 0.59 (p=0.72), respectively.

Figure 1 depicts the ROC plot for the combination of five variables that was associated with slightly higher AUC compared to the binary predictors alone. Thus, for PLWH the AUC was 0.71 (95%CI: 0.63-0.79) and for uninfected controls 0.65 (95%CI: 0.63-0.68), p=0.06. Redefining the criteria for airflow limitation (from LLN to GOLD II disease) resulted in a higher AUC (i.e. 0.77 (95%CI: 0.69-0.85) and 0.77 (95%CI: 0.75-0.80), p=0.98).

Discussion

Establishing a COPD diagnosis is important in order to initiate adequate risk factor modifications and potentially therapy. However, establishing a diagnosis in PLWH may potentially be impeded by competing risk factors and respiratory symptoms caused by other infectious and non-infectious respiratory diseases in the population. We showed that diagnostic performance of respiratory risk factors and symptoms (and a combination of these) in PLWH were relatively poor at discriminating airflow limitation but largely comparable to uninfected individuals.

To our knowledge no other studies have compared diagnostic performance of clinical characteristics in PLWH and uninfected controls. However, the multicenter Lung-HIV consortium evaluated diagnostic performance of clinical characteristics in PLWH for detection of any abnormal spirometry pattern (defined as obstructive: $FEV_1/FVC < 0.7$ and restricted $FEV_1/FVC \geq 0.7$ and $FVC < 80\%$ predicted) (13). This study also found poor diagnostic performance of all binary predictors but slightly lower AUC values than in the present study. Our data confirm these findings and show that the diagnostic performances of binary predictors are, however, similar or potentially better than in uninfected individuals.

The authors of the Lung-HIV consortium argued that screening with spirometry could potentially be warranted due to a high prevalence of airflow limitation and poor predictive capability of respiratory symptom in PLWH (13). However, no study performed in PLWH has directly assessed the effects of spirometry screening for COPD on morbidity, mortality, or patient reported outcomes. Thus, clinical guidelines in PLWH still have to rely on findings from the general population. Spirometry screening in the general population has been reviewed by the UK National Screening Committee (7) and by the USPSTF (8) and both institutions recommended against the use of spirometry screening. However, the importance of spirometry in establishing the diagnosis of COPD should not be undermined and spirometry is likely to be underutilized in many HIV settings, especially in resource-limited settings. Moreover, screening spirometry as part of a smoking cessation strategy may positively influence quit rates (14).

A number of studies in the general population have evaluated and externally validated combinations of risk factors and/or symptom-based questionnaires for COPD (11, 15-17). We additionally assessed a simple combination of five binary items (i.e., age ≥ 50 years, wheezing, dyspnea, sputum, cumulative smoking for ≥ 20 years) as these were associated with the highest AUC (0.72) in a previous study (11). The combination of these items yielded a similar and acceptable AUC (0.71) in PLWH but slightly lower AUC (0.65) in uninfected controls.

In conclusion, our findings indicate that active case finding based on respiratory risk factors and symptoms, as recommended in the general population (2), is likely to have at least the same diagnostic power in PLWH. Future studies should compare binary and weighted scores (potentially including HIV associated biomarkers of inflammation, immune activation and microbial translocation) for early detection of COPD in PLWH.

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Author contributions

All authors were responsible for concept and design. AR, TB, SDN collected the data. AR performed the statistical analyses. AR prepared the first draft of the manuscript and completed all revisions. All authors provided critical input at all stages of the preparation of the manuscript.

Declaration of interests

AR: No conflicts of interest. TB: Personal fees from Bristol Myers Squibb (BMS), and from Gilead, and non-financial support from BMS, and from Gilead. AM: Travel support, honoraria, speaker fees and/or lecture fees from Bristol-Myers Squibb, Gilead Sciences, ViiV HealthCare, Pfizer, Merck, BI and Wragge LLC. JG: Honoraria for consulting and presenting paid to his institution from Gilead, Abbvie, ViiV, BMS, MSD, Janssen, and Medivir. BGN: No conflicts of interest. JV: Honoraria for consulting and presenting from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Novartis. SDN: Unrestricted research grants from Novo Nordisk Foundation, Lundbeck Foundation,

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Table 1. Diagnostic performance of clinical characteristics to detect airflow limitation

	PLWH Sensitivity (%)	Controls Sensitivity (%)	PLWH Specificity (%)	Controls Specificity (%)	PLWH PPV (%)	Control PPV (%)	PLWH NPV (%)	Control NPV (%)	PLWH AUC (95%CI)	Control AUC (95%CI)	P-value*
Sputum	28.6	22.5	83.7	92.1	16.9	24.3	91.0	91.4	0.56 (0.50-0.63)	0.57 (0.55-0.59)	0.63
Chronic cough	26.4	15.0	88.6	94.1	21.4	21.4	91.1	91.2	0.58 (0.51-64.2)	0.55 (0.53-0.57)	0.20
Dyspnea	18.5	9.1	93.4	96.5	25.3	21.7	90.6	90.9	0.56 (0.49-0.63)	0.53(0.51-0.55)	0.10
Wheezing	47.2	33.3	80.9	86.0	22.7	20.3	92.8	92.3	0.64 (0.57-0.71)	0.60 (0.58-0.62)	0.09
Current smoking	52.6	24.3	73.7	88.5	19.2	20.0	92.9	90.8	0.63 (0.56-0.70)	0.56 (0.54-0.58)	<0.01
>20 pack-years of smoking	56.1	34.7	74.0	83.2	20.0	18.0	93.4	92.3	0.65 (0.58-0.72)	0.59 (0.57-0.61)	0.02
>30 pack-years of smoking	40.2	23.3	86.2	91.5	25.6	22.4	92.4	91.8	0.63 (0.56-0.70)	0.57 (0.55-0.59)	0.02
Self-reported COPD	17.6	12.8	98.6	99.2	59.4	65.6	91.0	91.0	0.58 (0.51-0.65)	0.56 (0.54-0.58)	0.29

Abbreviations: AUC, area under the curve; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NPV, negative predictive value; PLWH, people living with HIV; PPV, positive predictive value.

*Comparison of AUC values in PLWH and uninfected controls.

Figure 1. Receiver operating characteristics (ROC) in people living with HIV and uninfected controls for a combination of five clinical variables

A: Airflow limitation defined by FEV_1/FVC < lower limit of normal. P-value=0.06. B: Airflow limitation defined by $FEV_1/FVC < 0.7 + FEV_1$ -pred < 80% (GOLD disease II). P-value=0.98. The ROC for the sum (1=yes, 0=no) of five different dichotomized items (i.e. age ≥ 50 years, wheezing, dyspnea, sputum and ≥ 20 years pack years of smoking). Abbreviations: PLWH, people living with HIV.