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DOI:
10.1183/13993003.01613-2019

Document Version
Peer reviewed version

Citation for published version (Harvard):
Madan, A & Turner, A 2019, 'Identifying the at risk smokers: who goes on to get COPD?', *The European respiratory journal*, vol. 54, no. 4, 1901613. https://doi.org/10.1183/13993003.01613-2019

Identifying the at risk smokers: who goes on to get COPD?

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Keywords: Chronic obstructive pulmonary disease; emphysema; cigarette smoking; tomography, X-ray computed; prognosis; screening

Word count: 1496

Chronic obstructive Pulmonary Disease (COPD) is a common disease that predominantly affects smokers and is characterised by persistent and usually progressive airflow limitation(1). Whilst international bodies such as the Global Obstructive Lung Disease (GOLD) initiative have varied in their classification system for COPD severity over the years, there has long been recognition that pathologically(2) and clinically(3) relevant disease may be present before spirometry becomes abnormal – indeed GOLD included 'at risk' as a disease stage in early iterations of their documents on COPD. In addition there is debate on what constitutes early disease, in terms of chronology, versus what constitutes mild disease, in terms of either physiology or impact on the patient – these may not always be the same. For example, a patient who has developed COPD at a late age, through the aetiology of poor lung growth in early life(4) could have mild disease if symptom burden and physiology were not markedly impaired, but this is not early, since the processes driving the diagnosis have been present lifelong. Identifying those patients who have early disease which is likely to progress, particularly as we move toward an era of potentially disease modifying therapies is an area of great clinical need.

The research reported in this issue of the journal by Arjomandi et al [editorial team to insert reference for paper ERJ-02214-2018.R1] is important as it contributes to this debate, and may change the way clinicians prognosticate and predict progression to COPD. The study was conducted in part because inflammatory signals in symptomatic smokers' airway secretions have been reported whose pattern was consistent with COPD(5); this suggests that early pathological changes are present in these patients which are not detected by spirometry. Since only 20% of smokers are classified as having COPD, yet many are symptomatic, measurements other than spirometry may be required to describe their disease, and determine risk of progression to COPD. Several studies have suggested that small airways disease (SAD) is the earliest abnormality to occur in COPD (6, 7), perhaps because of altered tissue repair mechanisms (8). However emphysema can also occur prior to spirometric abnormalities, and when this occurs the extent appears to be a risk factor for respiratory death, even at low smoke exposures, or without a diagnosis of COPD(9). Consequently any study of patients at risk of progression to COPD needs to include a reliable method of assessing both SAD and emphysema. CT scanning is attractive in this regard since it can be used to quantify emphysema, typically using lung density from an inspiratory scan at total lung capacity, and also to measure SAD – a number of techniques have been used for this, of which parametric response mapping (PRM) (10) involving use of paired inspiratory and expiratory scans is now well known.

SPIROMICS is a multi-centre observational study designed to guide further development of treatment for COPD through characterising sub-populations over time(11). The paper in this issue [ERJ-02214-2018.R1] reports a post-hoc analysis of 849 current and ex-smokers (≥20 year pack history) with preserved spirometry within the SPIROMICS cohort, and specifically asks whether CT guided lung volumes defined by the ratio of residual volume to total lung capacity (RV_{CT}/TLC_{CT}) could predict future lung function decline and progression to COPD. The authors found that increased air trapping based on these CT-derived volumes predicts faster spirometric decline and progression to COPD, such that over 2.7 years of follow up, subjects with RV_{CT}/TLC_{CT} in the upper tertile had a faster rate of decline in FEV1/FEVC (0.66% per year (95%CI=0.06%-1.27%) , p=0.015) when compared to the lower tertile. They were also more likely develop spirometric COPD (odds ratio = 5.7, p <0.001) compared to the lower tertile, regardless of baseline characteristics such as baseline spirometry and smoking status. Whilst they were not able to report physiology confirming the RV/TLC ratio by plethysmography, other studies have shown a reasonable correlation between gas trapping on CT and this more traditional volume measure(12). When all the CT indices of air trapping were included in the model, including PRM of functional SAD and percent voxel on expiratory CT (as a measure of emphysema), only RV_{CT}/TLC_{CT}

remained significant, suggesting that the critical feature is SAD and not emphysema. Whilst SAD certainly appeared more important in these multivariate models the tables of characteristics show that at baseline emphysema was more severe as the RV_{CT}/TLC_{CT} tertile rose, such that both components probably play a role. Irrespective of the cause of gas trapping (due to SAD or emphysema) it appeared clinically important, in that those with the highest tertile of RV_{CT}/TLC_{CT} had a lower exercise capacity, as measured by 6 minute walk test distance, which exceeded at least one definition of the minimum clinical important difference for this measure(13). Interestingly no association was seen with exacerbations of COPD requiring hospital admission for any of the three tertiles; this may be explicable because lower FEV1 is a major factor in admission(14) and any patients who moved from normal spirometry to COPD within the short follow up period then had mild disease. Consistent with this interpretation only 36 subjects had severe exacerbations, and follow up FEV1 in the highest risk group was 94% predicted. Furthermore symptomatic deterioration was found using only one of the three SPRIROMICS study questionnaires, with the other two questionnaires showing non- significant trends. Again this finding probably reflects the mild disease present even at follow up, alongside the fact that by the time symptoms develop, disease may no longer be early, even if it is mild.

The study has several strengths. Firstly the authors carefully considered the validity of their CT scan derived lung volumes by selecting those whose CT derived vital capacity matched the slow FVC obtained at spirometry for their primary analysis; this resulted in 618/814 subjects with high quality complete data being analysed. Whilst this process excluded a significant proportion of patients subsequent sensitivity analysis demonstrated that this had no impact on the direction of association of RV_{CT}/TLC_{CT} with subsequent decline. They also considered the impact of a number of known risk factors for lung function decline, such as active smoking, amount of smoke exposure and bronchodilator reversibility, by including these features in either multivariable or sensitivity analyses. These factors are known to influence decline not only in COPD(15) but in other 'at risk' groups, such as those with a genetic susceptibility to COPD, like alpha 1 antitrypsin deficiency(16) or who are exposed to biomass smoke(17). These analyses demonstrated that smoking status and pack years smoked did not influence decline; considering that the SPIROMICS cohort all have significant smoke exposure the authors concluded that after 20 pack years exposure there are some subjects who are predisposed to decline ('susceptible smokers'), and that they might be identified by their higher $RV_{CT}/TLC_{CT.}$ None of the other confounders markedly influenced the primary reported association of gas trapping with decline.

However, as with many cohort studies, follow up data appeared more difficult to collect than baseline; consequently only 496 out of 618 subjects had a follow up spirometry result. This equates to nearly 20% of subjects lacking follow up spirometry. Furthermore, of the 496 subjects, 44 only had one follow-up spirometry result yet two or more spirometry results are generally required over this time period to see a reliable trend in lung function decline. This meant that only 157 of 618 subjects in the highest RV_{CT}/TLC_{CT} tertile had three follow up spirometry results over which to calculate decline, with 122 having no follow up spirometry results. The reduction in numbers naturally results in loss of power, and whilst it does not diminish the significance of their findings, it suggests some caution in interpretation is required, and that replication will be important. In addition the median follow-up for the reported data was only 2.7 years; it will be important to see outcome data after a longer period of follow-up, given the chronicity and slow progression generally seen in COPD. The authors recognized this when discussing the limitations of their work.

Finally, it is worth considering the messages this paper brings to clinical practice. Clinicians, particularly in primary care, would welcome a way to identify which smokers should be more closely followed up so that treatment for significant COPD can be instituted quickly and through so doing

deterioration due to deconditioning and exacerbations reduced. Whilst the authors have demonstrated that CT guided lung volumes can accurately predict progression to COPD, the feasibility of using this technique in clinical practice due to cost and radiation exposure is questionable. Additional research into techniques to identify gas trapping using measures possible in primary care will therefore be important. However, in the era of CT screening for lung cancer, which generally occurs in smoke exposed people, due to their higher risk of malignancy relative to never smokers, many countries will have imaging data available on large numbers of subjects at risk of progression to COPD; using these visits (and CT images) for more than just lung cancer screening(18) could enhance existing cost-effectiveness(19) whilst also being acceptable to patients.

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