



Letter to the Editor

Is an Early Diagnosis of COPD Clinically Useful?

¿Es clínicamente útil un diagnóstico temprano de EPOC?

Dear Editor,

An early diagnosis of a disease among people who feel well, reducing future morbidity and mortality, is important in many chronic diseases, especially in malignancy. An early diagnosis should benefit patients. However, even in such disorders, an early diagnosis can turn indolent pathologies into illness and screening can result in an excess of diagnoses.¹ This is over-diagnosis, a growing problem in high-income countries. It can be considered when the treatment of the diagnosed conditions, sometimes indolent situations that would never cause patients harm, cannot improve patients' outcomes, exposing them to unnecessary risks and therefore being potentially harmful.^{2,3} Chronic Obstructive Pulmonary Disease (COPD) represents one of the most significant health problems at international level. It is the only leading cause of death with rising mortality and morbidity. COPD is considered to be an underdiagnosed and undertreated disorder, especially in its mild and moderate degrees. Although the need for an early detection makes sense, when can an early diagnosis become an over-diagnosis?

Over-diagnosis and misdiagnosis represent two different concepts.⁴ Over-diagnosis means identifying problems that were never going to cause harm.³ It has two major causes: 'over-detection' and 'over-definition'. Misdiagnosis consists in giving a wrong diagnosis to a person who is really ill.³ In primary health care, many COPD diagnoses are made without a spirometry confirmation, using inadequate algorithms and with difficulties establishing the correct differential diagnoses.⁵

Spirometry has an important role in the early diagnosis of COPD. In the early stages of the disease the clinical manifestations are inconstant, usually minor and not valued by patients. Symptoms are frequently accepted as normal or expected, attributed to smoking, and patients do not seek medical attention until the disease is more advanced and their symptoms are already compromising daily activities. Although we acknowledge that the early pathological changes in COPD are not captured by spirometry,⁶ we do not currently have any marker to detect early onset of the airway disease, though, the use of spirometry, depending on the values of reference used, may be a cause of over-diagnosis, especially in the elderly.⁷

Some authors argue that pharmacological interventions in the early stages of COPD, when a faster disease progression is known to occur,^{8,9} are of significant importance as they could delay its progression, like in many other chronic disorders. However, there is a wide range in FEV₁ decline in patients with COPD, and there is no tool to identify patients who would benefit from treatment to prevent the deterioration of respiratory function. Moreover, no markers of the disease are known to predict which patients with a recent onset of the disease will progress to a greater severity.¹⁰ Until now, the presence of symptoms in mild COPD – a significantly

different concept than early COPD – is the best predictor of acceleration in FEV₁ decline. Asymptomatic patients with mild airflow limitation do not present a faster decline in FEV₁ neither have worse quality of life than healthy individuals.¹¹ However, they frequently present mild unreported exacerbations that impact patients' health status, and can be related to a small excess of FEV₁ decline.

An early diagnosis of COPD in people who feel well requires a significant amount of time, effort and costs. The US preventive Services Task Force (USPSTF) did not find evidence that screening for COPD using spirometry in asymptomatic people improves health outcomes (health-related quality of life, morbidity or mortality), and four of five trials assessing the effects of screening in smoking cessation did not report significant differences in abstinence rates. Therefore, the USPSTF concludes with moderate certainty that screening for COPD in asymptomatic people has no net benefit.¹² Many other published guidelines also recommended against screening for COPD in asymptomatic patients. The major goals in the treatment of COPD are the reduction of symptoms and exacerbations, and improvement of exercise tolerance and health status. However, the evidence achieved by most of the published RCTs related to pharmacological therapy can be applied only to patients with a severe or a very severe disease, because they do not use asymptomatic participants. Moreover, adherence to inhaled medications in COPD patients is strongly related to symptoms and to the functional severity of the disease.¹³ A good adherence profile is then not expectable in patients with early disease, or with mild COPD.

Lung cancer screening with low-dose computed tomography can be useful to improve early-stage detection, increasing resectability and survival. COPD and cigarette smoking are two known independent risk factors for lung cancer. Because of that, some authors argued that the early diagnosis of COPD in smokers can help to select candidates for lung cancer screening.¹⁴ It is infrequent to see a normal spirometry in patients with lung cancer.¹⁵ Calabrò et al. demonstrated that even a small reduction in FEV₁% is a significant predictor of increased risk for lung cancer. Airflow obstruction can be understood as a surrogate marker for carcinogenic damage of the airways,¹⁶ and screening for lung cancer can be done using a decrease in FEV₁%. These could be an important argument to support the importance of an early diagnosis of COPD.

We need an early diagnosis with demonstrated benefits to the patients but, without an accurate knowledge on markers of the disease activity, mainly in the early stages of COPD, guiding therapy and helping to understand the different accelerated declines in lung function, an early diagnosis can turn out to be an over-diagnosis.

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Microbioma de la vía aérea inferior y cáncer de pulmón



The Lower Airway Microbiome and Lung Cancer

Estimado Director:

En un reciente editorial, Garrido-Martín y Paz-Ares¹ comentan las novedosas aportaciones del estudio del microbioma en pacientes con cáncer de pulmón, fundamentalmente sobre las interesantes expectativas de su manipulación y el potencial efecto en la respuesta terapéutica. En el editorial también se menciona, aunque de forma breve, la posibilidad de identificar determinados gérmenes que podrían ser utilizados como biomarcadores diagnósticos o pronósticos en el cáncer de pulmón. Varios estudios del microbioma respiratorio han sugerido la existencia de cambios característicos en las poblaciones bacterianas de la vía aérea en estos pacientes^{2,3}. Aunque existen algunas diferencias en los estudios, en general *Granulicatella*, *Streptococcus* o *Veillonella* se han encontrado con mayor frecuencia en muestras respiratorias de pacientes con cáncer de pulmón^{2,3}. En este sentido, nuestro grupo ha realizado un estudio utilizando muestras obtenidas por broncoscopia con cepillado protegido en el tumor y en la misma zona del pulmón contralateral de pacientes con cáncer de pulmón y en controles sin enfermedad maligna³. Mediante la secuenciación masiva del ADN bacteriano obtuvimos que la microbiota de la vía aérea inferior era similar en la zona del tumor y en el segmento equivalente del pulmón contralateral, pero diferente de la microbiota detectada en los pacientes sin cáncer. Estas diferencias, como apuntaban Garrido-Martín y Paz-Ares¹ podrían tener aplicación como biomarcadores diagnósticos. En nuestra experiencia, la identificación de *Enterococcus*, *Capnocytophaga* y *Actinomyces* tenían una eficiencia diagnóstica para malignidad del 70%, y *Microbispora* permitía excluir el cáncer con una eficiencia del 78%³.

Los estudios realizados para identificar gérmenes como biomarcadores en estos pacientes emplean diferentes métodos e incluyen en general un número relativamente bajo de pacientes; además se conoce que los resultados también pueden variar por alteraciones del microbioma respiratorio en distintas regiones del mundo⁴, por lo que todavía no es posible extraer conclusiones clínicas. Sin embargo es indudable que el estudio del microbioma respiratorio supone una novedosa aproximación tanto al estudio de la patogenia de diversas enfermedades como a posibilidades diagnósticas, o como señalan Garrido-Martín y Paz-Ares¹, a modificar la respuesta terapéutica del cáncer de pulmón.

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