What happens between first symptoms and first acute exacerbation of COPD – observational study of routine data and patient survey

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Scientific summary

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Scientific summary

Background

Chronic obstructive pulmonary disease (COPD) affects nearly 400 million worldwide – over a million in the UK – and is the third leading cause of death. Despite this, there is limited understanding of what prompts a diagnosis, how long this takes from symptom onset and the different approaches to clinical management taken by primary care professionals. This is particularly true regarding people with comorbidities such as asthma and heart failure (HF) that can also cause breathlessness.

Objectives

Map out the clinical management and NHS contacts from symptom presentation to COPD diagnosis and first acute exacerbation, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (for some patients the latter two will be the same event); investigate whether and how this varied in three cohorts since 2006; rank predictors of the first AECOPD in importance and assess whether and how this changed over time; construct and validate risk prediction models for the first AECOPD.

Methods

The project involved the quantitative analysis of an existing database and a new survey. The main component used the Clinical Practice Research Datalink (CPRD), which collects deidentified patient electronic health records from participating general practitioner (GP) practices; its Aurum version includes healthcare records from GP practices using EMIS® software, representing around 13% of the population in England. It includes patient-level data on demographics, tests, symptoms, diagnoses, therapies, prescriptions and referrals to secondary care. Patient-level data from these practices were linked by CPRD staff to the Office for National Statistics death register, Hospital Episode Statistics and Index of Multiple Deprivation at small area level.

We included all individuals aged over 35 years with COPD diagnosed between 1 April 2006 and 31 March 2007 (cohort 1) and between 1 April 2016 and 31 March 2017 (cohort 2); a smaller COVID-era group for March–August 2020 made up cohort 3. For each patient, the index (diagnosis) date was defined as the first record of COPD, either in primary care records via SNOMED-CT codes or in hospital admission data via *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision* codes. Patients had to have at least 1 year's registration with the GP before the diagnosis date. Patient characteristics were described for the year up to and including the diagnosis date; GP actions were also described in the year before and since diagnosis. The first AECOPD was identified using our group's published algorithm and was restricted to hospital admissions to reliably capture the most serious ones. Much of the analysis was descriptive, including cumulative incidence plots for the time to first AECOPD by cohort. GP actions before diagnosis were compared with the National Institute for Health and Care Excellence (NICE) guidelines, which recommend spirometry, chest X-ray, full blood count (FBC) and the calculation of body mass index (BMI). These 'routes to diagnosis' analyses were stratified by pre-existing HF and asthma, conditions that share some symptoms and that could cause diagnostic confusion. Multilevel models assessed the variation between GP practices in the proportion of patients receiving spirometry in the 6 months prior to or after diagnosis; funnel plots were used to count statistical outliers at 2 and 3 standard deviations (SD) from the mean. Prescriptions for the main classes of medication were noted for the year following diagnosis. A set of Fine and Gray regression models quantified the association between patient characteristics, GP actions and first AECOPD in patients not diagnosed via an AECOPD, accounting for the competing risk of death from non-COPD

causes: model 1 contained only patient factors, model 2 additionally contained pre-diagnosis GP actions and model 3 also included post-diagnosis GP actions. Population attributable risks (PARs) were calculated for statistically significant risk factors. The focus for the reporting of the model outputs was on the model containing patient characteristics and pre-diagnosis GP actions.

We developed an online survey to investigate COPD patients' retrospective perceptions of their initial symptoms, what they did after developing those symptoms, what kind of professional advice was sought and year of diagnosis in order to distinguish between COVID and pre-COVID eras. It was designed jointly through a series of discussions by the project team at Imperial College London, which included researchers and patient representatives, and the teams at Asthma + Lung UK and the Taskforce for Lung Health, including its own patient advisory group. This was administered via the charity and GPs contributing to CPRD.

Results

Cohort 1 had 31,676 patients, cohort 2 had 37,393 and cohort 3 had 4752. Overall, the mean age was 68.3 years (SD 12.0), and 47.3% were female; the age–sex mix did not change over time with 82.7% being current or ex-smokers. Common comorbidities included hypertension, anxiety, depression, asthma, stroke, diabetes and renal disease, with an average of nearly four per patient. Around three-quarters were diagnosed in primary care, with a slight fall in this proportion in cohort 3. Those diagnosed this way were older, with lower blood pressure and had more comorbidities, with higher levels in recorded prevalence for anxiety, depression and diabetes being among the most notable. Nearly half of all patients had had a lower respiratory tract infection recorded in the 5 years before diagnosis, with presentations for other symptoms also common.

Compliance with NICE diagnostic guidelines was slightly higher in cohorts 2 and 3 for all patients; 35.8% (10.0% in the year before diagnosis) had all four elements met overall. Spirometry in the year before diagnosis rose from 55.7% in cohort 1 to 63.8% in cohort 2 but then fell to 37.4% in cohort 3; around a third had a chest X-ray, half had a FBC and half had a BMI measurement in this time. The use of pre-diagnosis echocardiography, cardiology referral and B-type natriuretic peptide (BNP) testing rose considerably over time, though BNP recording remained low despite its now widespread availability. In the 5 years before diagnosis, 36% were prescribed inhaled steroids (similar for each cohort and for oral steroids); 61% were prescribed short-acting beta agonist (SABA); 10% long-acting muscarinic antagonist (LAMA) (this rose to 20% for cohort 3). Compared with all patients combined, patients diagnosed through an emergency hospitalisation were less likely to have had pre-diagnosis spirometry in cohorts 1 and 2, but equally likely in cohort 3. They were much more likely to have had a chest X-ray and FBC in each cohort.

In cohort 1, practices had a median of 23 new COPD patients, with 18 diagnosed in primary care; these figures were 28 and 21 for cohort 2. There was considerable variation between practices in spirometry use, with median odds ratios of 1.5 or more. For patients diagnosed in primary care, 24.5% of practices in cohort 1 and 19.7% in cohort 2 were funnel plot outliers at 2 SD.

The survey on the charity website had 156 responses by COPD patients, of whom 124 (79.5%) were female and 82.7% were aged between 45 and 74 years. Many respondents had not heard of the condition, hoped the symptoms would go away, and identified healthcare-related barriers to earlier diagnosis such as difficulty in getting an appointment and the impression of not always being taken seriously by staff. The response rate from CPRD GPs was too low to allow analysis.

In the year following diagnosis, there were notable changes in prescribing from cohort 1 to 2, such as increases in LAMA (21.7–46.3%) and long-acting beta agonist (10.1–15.9%) and falls in short-acting muscarinic antagonist (12.4–2.1%) and inhaled corticosteroids (52.6–41.1%). SABA use changed little. These were maintained into the COVID era. Triple therapy rose from 2.9% in cohort 2 to 11.1% in cohort 3. Around four in five patients in each cohort were offered the influenza vaccine, with two-thirds

receiving it from the practice. Documented pulmonary rehabilitation (PR) rose from just 0.8% in cohort 1 to 13.7% in cohort 2 and 20.9% in cohort 3. Smoking cessation drug prescription fell over time, whereas advice fluctuated.

For all patients combined, the median time to first AECOPD in those who had one was 1.4 years in cohorts 1 and 2. This was generally slightly shorter in patients with HF and/or asthma. Those with HF, but not those with asthma, had much higher exacerbation rates. The all-cause death rate was notably higher for cohort 3 than the other two. The AECOPD prediction models consistently identified a number of predictors, including age (but not sex), deprivation, COPD severity, current smoking and various comorbidities such as osteoporosis, asthma and depression; other comorbidities, such as HF and diabetes with complications, were less consistently significant. Some medications, particularly LAMA, were associated with higher hazards. In the model including post-diagnosis GP actions, annual COPD review [cohort 2 adjusted hazard ratio (aHR) 0.63, 95% confidence interval (CI) 0.58 to 0.69], post-diagnosis spirometry (cohort 2 aHR 0.83, 95% CI 0.78 to 0.88) and flu vaccination (cohort 2 aHR 0.56, 95% CI 0.53 to 0.60) all had hazards < 1, but we did not find any significant association for specialist referral (cohort 2 aHR 1.10, 95% CI 0.99 to 1.20) or PR (cohort 2 aHR 1.04, 95% CI 0.96 to 1.13). Discrimination was moderate, with *c*-statistics of around 0.70 for models without post-diagnosis GP actions. The highest *c*-statistic was 0.81 and was obtained for model 3, with post-diagnosis GP actions, at 6 months of follow-up. Calibration was good for all models. For cohort 2, when the model with post-diagnosis GP actions was simplified to include only predictors with $p < 0.05$, the three most important predictors in terms of their PARs were being a current smoker (32.8%), Global Initiative for Obstructive Lung Disease severity (30.6%) and deprivation (15.4%). The highest PARs for variables with aHRs < 1 were COPD review (–27.3%) and flu vaccination (–26.6%). For a typical local population with 5000 COPD patients, these PARs translate into average potential annual cost savings of £193K for COPD review and £188K for flu vaccination.

Conclusions

There have been several improvements over time in NICE diagnostic guideline compliance, prescribing and referral for PR, but much more improvement is desirable, and there remains much variation between GP practices in spirometry use. There is also much unawareness of the condition among UK adults at risk of it. Data currently available in GP information technology systems are not enough to predict someone's first AECOPD with sufficient accuracy to guide shared decision-making.

Our recommendations for research are: (1) understand how and develop approaches to overcome NHS and patient barriers to earlier diagnosis; (2) seek strategies to reduce unwarranted variation in spirometry use between practices; (3) repeat the analysis on more data since March 2020 and with longer follow-up; (4) assess variations in prescribing between practices; and (5) evaluate the statistical reliability of practice-level spirometry as a potential quality indicator.

Study registration

This study is registered as Researchregistry.com: researchregistry4762.

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