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Original Article

Characterization of circadian COPD symptoms by phenotype: Methodology of the STORICO observational study

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. The symptoms of COPD are troublesome, variable, can occur during all parts of the 24-h day and have a substantial impact on patients' health status, quality of life and healthcare resource utilization. Reducing symptoms, improving health status and increasing physical activity are major goals in the management of stable COPD. In order to provide effective, patient-oriented care, patients should be evaluated on the basis of lung function, frequency of symptoms and patient-perceived impact of symptoms on their lives and treatment decisions made on a case-by-case basis.

The identification of COPD phenotypes is an evolving debate and literature data about the circadian variation of COPD symptoms according to phenotypes are nowadays lacking. The ongoing STORICO (*STudio Osservazionale sulla caratterizzazione dei sintomi delle 24 ore nei pazienti con BPCO*) study (NCT03105999) is aimed to describe by clinically defined phenotypes the frequency and 12-month evolution of early-morning, day- and night-time COPD symptoms in a cohort of 600 Italian patients with stable COPD. Secondary objectives include the description of the 12-month variation of outcomes of interest according to phenotypes and of the healthcare resources utilization (overall and by phenotype) during 12-month observation. An exploratory analysis will be conducted aimed to phenotype COPD patients in an alternative researcher-independent way based on circadian pattern of symptoms combined with measures of respiratory function, health-related quality of life and comorbidity. The present paper describes the methodology of the STORICO study.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide [1,2]. Among the factors which can contribute to this disease the following can be listed: bronchial disorder (chronic bronchitis), pathological condition of the small airways and parenchymal disorders, such as pulmonary emphysema. Pulmonary component of COPD is characterized by chronic airflow

limitation usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases [3]. Although tobacco smoking is the most important risk factor for both the development and progression of COPD, it is not the only one, with other risk factors such as asthma, exposure to ambient pollutants in the home and workplace and respiratory infections also being important, especially in developing countries [4–6].

The chronic obstruction, characteristic of COPD, results from airflow limitation throughout the whole bronchial tree as well as from loss of elastic recoil and ensuing hyperinflation and worsening small airways obstruction.

COPD symptoms are quite common (according to Kessler [7], 92.5% of patients reported experiencing at least one of the following symptoms in the 7 days prior to interview: breathlessness, phlegm, cough,

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wheezing or chest tightness) and their circadian variation is known: 62.7% of patients perceived daily/weekly variability in one or more symptoms [7]. Symptoms seem to be worst in the morning: 71% of patients report phlegm in the morning, 54–60% cough, 41–50% dyspnea, 45% chest tightness and 43% wheezing [7–9]. Morning is the worst time of day particularly in patients with severe COPD (46% according to Partridge [10]). Early morning symptoms impact on patients' daily normal activities [7–12] and are associated with worse health status and higher risk of COPD exacerbations [11–13].

The second most important period of impairment is the night, with an increase in respiratory symptoms, such as wheezing or chest tightness, and disturbed sleep quality [9], the prevalence of nocturnal symptoms and symptomatic sleep disturbance exceeding 75% in patients with COPD [14]. Patients with night-time symptoms have significantly worse health status, more sleep disturbances and higher healthcare resource utilization than patients without them [15].

The ASSESS study showed that symptoms were more common in the early morning and day-time versus night-time (81.4%, 82.7% and 63.0%, respectively) and that symptom severity was comparable for each period assessed. In the week before baseline, 56.7% of patients had symptoms throughout the whole 24-hour day (3 parts of the day) [16].

Progressive dyspnea, chronic cough, decreased exercise tolerance and excessive sputum production can impact considerably on patients' quality of life [11]. Diverse studies have demonstrated that patients with more severe disease stages present poorer health-related quality of life (HRQoL) [17,18] and the progressive deterioration and disability experienced by patients with COPD lead to a worsening in their HRQoL and a subsequent increased healthcare resource consumption [19].

The symptoms of COPD are therefore troublesome, variable, can occur during all parts of the 24-h day, and have a substantial impact on patients' health status and quality of life. Reducing symptoms, improving health status and increasing physical activity are major goals in the management of stable COPD [20]. To provide effective, patient-orientated care, patients with COPD should be evaluated on the basis of lung function, frequency of symptoms and patient-perceived impact of symptoms on their lives. In order for the most appropriate treatment to be selected, patients should be assessed and treatment decisions made on a case-by-case basis [21–27].

The concept of phenotype for COPD has been recently developed, resulting in the definition of phenotype as “the attributes of the disease which alone or in combination describe the differences between individuals with COPD in relation to parameters with clinical significance” [28]. The concept of phenotype has resulted in the definition of different types of patients with prognostic and therapeutic significance; it is possible to prescribe a more personalized treatment according not only to the severity of the airflow obstruction, but also conditioned by the clinical phenotype [24–27].

The identification of COPD phenotypes is an evolving debate. Hurst [29] supported the hypothesis that patients who are more subject to frequent exacerbations, some of whom have milder disease, have a distinct susceptibility phenotype that is relatively stable over time and can be identified on the basis of the patient's recall of previously treated events. García-Aymerich [30] identified severe respiratory, moderate respiratory and systemic COPD phenotypes while Spanish COPD guidelines GesEPOC found out the exacerbator, mixed COPD, emphysema and chronic bronchitis phenotypes [31]. Roche confirmed the presence of a chronic bronchitic phenotype [12], associated with an increased risk of exacerbations [32] and with accelerated lung function decline and increased morbidity [33]. In patients with COPD, the priority should be to define the prevalent underlying disease, generally, identified by clinical, radiological (chest X-ray) and functional assessments or by a more extensive work-up including high-resolution computed tomography lung scan, if necessary. Based on different underlying disease, namely prevalent chronic bronchiolitis versus prevalent pulmonary

emphysema, the effect of anti-inflammatory treatments on top of long-acting bronchodilators is different in terms of improvement in function, symptoms, quality of life and prevention of exacerbations. In addition, the functional decline is differently affected by treatment, the all-cause and respiratory mortality is different in long-term follow-up and finally the clinical phenotypes and some comorbidities tend to cluster differently [34].

Recently, several COPD phenotypes have been identified and validated against clinical outcomes or response to treatment including: (1) alpha-1 antitrypsin deficiency that may respond to augmentation therapy, (2) emphysema/hyperinflation that is responsive to lung volume reduction surgery and (3) frequent exacerbators who respond to therapies reducing exacerbation frequency [35]. Santus and collaborators [36] showed that pulmonary rehabilitation in patients with COPD has a positive effect on lung diffusing capacity (DLCO) regardless of the severity of disease and that changes in DLCO seem to depend on the patient's phenotype and endotype.

Even if frequency of COPD symptoms has been extensively analyzed, literature data about their circadian variation and their evolution according to phenotypes are extremely scarce.

For this reason, we are conducting in a cohort of Italian outpatients with stable COPD the STORICO (STudio Osservazionale sulla caratteRizzazione dei sintomi delle 24 ore nei pazienti con BPCO) study (NCT03105999) aimed to describe the frequency of early-morning, day- and night-time COPD symptoms at enrolment and their 12-month frequency and evolution according to phenotypes.

The evaluation of the association between early-morning, day- and night-time symptoms frequency at enrolment and dyspnea level, disease severity, quality of life, physical activity, quality of sleep, frequency and severity of exacerbations, level of depression and anxiety is the cross sectional secondary objective. Longitudinal phase's secondary objectives include: (ii) to describe the 12-month variation of dyspnea level, quality of life, physical activity, quality of sleep, frequency and severity of exacerbations, level of depression and anxiety according to phenotypes measured at enrolment and (iii) to describe (globally and by phenotypes) the healthcare resources utilization during 12-month observation.

The present paper describes the methodology of the STORICO study.

2. Materials and methods

2.1. Study design

STORICO is an Italian observational cohort multicentre study conducted in 40 pneumology centers. Visits' schedule is shown in Fig. 1. The enrolment started on February 2016 and the study is currently ongoing.

2.2. Subjects

Subjects of any gender aged ≥ 50 , current or ex-smokers with a smoking history of ≥ 10 pack-years, with a diagnosis of stable COPD since at least 12 months according to the GOLD 2014 criteria (stages A

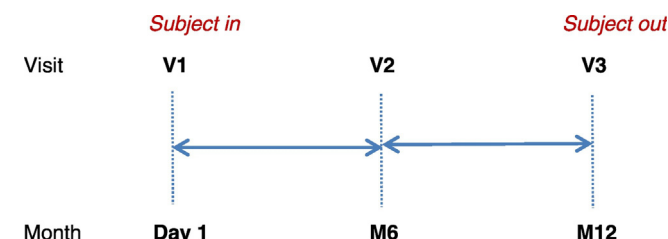


Fig. 1. Visits' schedule of the STORICO study.

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