Clinical Epidemiology of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is responsible for early morbidity and high mortality and significant costs to health systems. Smoking remains the main risk factor for COPD but additional factors, such as indoor and outdoor air pollution, occupational exposure and genetic susceptibility are increasingly recognized. Th e burden of COPD has been difficult to estimate owing to the multiple definitions applied, with variations between estimates of prevalence exceeding 15%. Definitions based on objective spirometric measurements have yielded higher prevalence estimates than patients' self-report of a clinical diagnosis of COPD. Th e Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed a physiologic definition of COPD characterized by airflow limitation that is not fully reversible (post-bronchodilator FEV1/FVC < 0.70). Many authors have argued against this fixed ratio definition and advocate the use of a "lower limit of normal" criterion to define COPD in order to avoid overdiagnosis of the disease in the elderly. Despite controversies, the definition proposed by GOLD is unambiguous, easily remembered by clinicians, reproducible in different settings and suitable for cross-sites comparisons. Recently, two multinational studies adopted the GOLD definition to provide standardized population-based estimates of the prevalence of COPD in adults aged 40 years or over throughout the world. These estimates varied between 11.4 and 26.1% in the international BOLD study and between 2.6% and 7.1% in the five Latin American cities of the PLATINO study. Although debate on COPD definition is ongoing, the burden of the disease is high and growing. The major challenge in coming years will be to stop the smoking epidemic, particularly in developing countries, and to increase physician knowledge of the disease favouring an early diagnosis.

PALAVRAS-CHAVE: CHRONIC OBSTRUCTIVE PULMONARY DISEASE, SPIROMETRY, PREVALENCE, BURDEN

EPIDEMIOLOGIA CLÍNICA DA DOENÇA PULMONAR OBSTRUTIVA CRÓNICA

RESUMO

A nível mundial, a morbilidade e mortalidade atribuíveis à doença pulmonar obstrutiva crónica (DPOC) têm vindo a aumentar e, actualmente, esta doença assume-se como uma importante ameaça económica e social. O tabagismo é o factor de risco quantitativamente mais importante e a poluição interior e exterior, a exposição ocupacional e a susceptibilidade genética têm sido reconhecidos como factores de risco adicionais. A prevalência de DPOC a nível populacional tem sido difícil de estimar devido à utilização de múltiplas definições. A variação das estimativas de prevalência é superior a 15% e as definições baseadas na espirometria apontam para valores mais elevados do que a auto-declaração do diagnóstico prévio de doença. A *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) propôs uma definição fisiológica da doença caracterizada por uma obstrução aérea não completamente reversível (FEV1/FVC<70%, após broncodilatador). Criticando esta definição assente numa razão fixa, muitos autores advogam a utilização do critério baseado no "limite inferior do normal" para definir DPOC, na tentativa de diminuir o sobrediagnóstico nos idosos. Apesar da controvérsia, a definição proposta pelo GOLD é clara, fácil de memorizar, reprodutível em diferentes contextos e adequada para fazer comparações entre regiões. Esta definição foi recentemente adoptada por dois estudos multinacionais com o objectivo de obter estimativas padronizadas de base populacional em adultos com idade igual ou superior a 40 anos. As estimativas variaram entre 11,4 e 26,1% no estudo BOLD e entre 2,6 e 7,1% nas 5 cidades latino-americanas do estudo PLATINO. Independentemente do debate acerca da definição de DPOC, é indiscutível que a carga atribuível à doença é elevada e tem vindo a aumentar. No futuro, o principal desafio é combater a epidemia tabágica, em particular nos países em desenvolvimento, e promover o diagnóstico mais precoce por parte dos clínicos.

KEY-WORDS: DOENÇA PULMONAR OBSTRUTIVA CRÓNICA, ESPIROMETRIA, PREVALÊNCIA

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INTRODUÇÃO

Chronic obstructive pulmonary disease (COPD) is a major health problem throughout the world[1], assuming epidemic proportions. It has been increasingly recognized as an impor-tant cause of premature death and disability, resulting in a tremendous economic and social burden[2,3]. In 2004, COPD was the fourth leading cause of death worldwide, accounting for 3.02 million deaths, 3.5% of the total in high- and low-income countries and 7.4% in middle-income countries[4]. During the same period, 1.9% of disability-adjusted life years (DALYs) were attributable to this condition[5]. Although a substantial proportion of COPD cases can be attributable to other exposures[6], cigarette smoking is by far the most important causally-related risk factor for the disease in the western world and it is becoming a growing and widespread habit in developing countries[7-9]. Based on current trends[10] and taking into account the expected aging of the world's population[11,12], the anticipated increases in smoking rate[13] and the decline in competing causes of death, COPD is projected to be the third leading cause of death and to rank fifth in the global burden of disease in 20205,[14].

Currently, direct and indirect costs of COPD treatment and disability represent a major global threat to health care systems and economies[15-17]. This scenario emphasizes that the implementation of preventive measures is an urgent public health priority, particularly in developing countries where an epidemiologic and demographic transition is ongoing very fast[18]. Reflecting the preventable and treatable nature of COPD, multiple guidelines on prevention and management of the disease have been published, aiming at improving awareness of disease and its risk factors, disseminating available treatment options for patients with established disease and encouraging continuous research in this area[1,19,20]. Despite these efforts, COPD is underdiagnosed and undertreated and estimates suggest that about one fifth of "healthy" adult smokers aged over 40 years actually have unrecognized disease[21].

DEFINITION AND CLASSIFICATION OF COPD

COPD is a relatively new term for an old disease presenting with different phenotypes[7,22]. The definition of COPD recently proposed by the Global Initiati-

ve for Chronic Obstructive Lung Disease (GOLD)[1] emerged from the need to unify several imprecise definitions that have proliferated over the years, based on different criteria. Historically, COPD has been defined clinically as chronic bronchitis and pathologically as emphysema[7]. More recently, a physiological definition based on spirometry has become consensual and is being increasingly used in epidemiological studies to objectively assess airflow limitation. The working definition established by GOLD and subsequently adopted by other international scientific societies[20] states that COPD is "a preventable and treatable disease state with some significant extrapulmonary effects" and "its pulmonary component is characterized by airflow limitation that is not fully reversible."[1]. Spirometry is considered the gold-standard for accurate and reproducible measurement of lung function and post-bronchodilator testing is essential to identify not fully reversible airflow obstruction and to classify disease severity[1]. According to currently adopted criteria, airflow limitation is defined as a post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV1/FVC) ratio lower than 70% and classification of COPD severity is based on the thresholds presented in **Table 1**. This "fixed" ratio criterion used to define obstruction is a generalized standard that has the advantage of allowing comparisons across different populations. Notwithstanding, considering the linear decline of FEV1/FVC ratio that normally occurs with age[23,24], there is some concern that its use may led to overdiagnosis of COPD in healthy elderly individuals[25-27]. Conversely, young subjects with lung functional impairment could be underdiagnosed[28,29]. Moreover, the specific spirometric cut-points applied to categorize stages of disease are used for simplicity and have not been clinically validated[3], undoubtedly promoting some degree of misclassification.

To overcome these shortcomings and minimize misclassification of older and younger subjects, some experts have proposed the adoption of a "lower limit of normal" criterion (the bottom 5% of the normal distribution of FEV1/FVC in a healthy reference population) to define COPD[30]. This definition is currently considered in some guidelines[32] but debate continues about whether this approach misclassifies as "normal" patients who are at increased risk for death and COPD-related hospitalization and who might benefit from treatment[23]. This risk is much higher among patients classified in GOLD stage II or above. Thus, besides being a practical threshold to identify clinically relevant disease, a FEV1 lower than 80% of predicted seems to convey some prognostic information[23]. The need of post-bronchodilator spirometry data to identify airflow limitation is another controversial issue related to disease classification. Strictly, GOLD criteria require the use of post-bronchodilator lung volumes because there is evidence that 20-30% of a population labeled as "obstructed" pre-bronchodilator will meet criteria of reversibility[33,34]. However, pre-bronchodilator spirometry is valuable in predicting mortality and morbidity outcomes in epidemiological studies[34,35]. The usefulness of looking at reversibility in epidemiological studies is still questioned by some authors arguing that there are no data supporting the superiority of post-bronchodilator lung function over pre-bronchodilator lung function in predicting mortality and other adverse outcomes[15].

Alternative classification schemes of COPD were suggested based on the acknowledgment of in-between phenotypes and manifestations of the disease, including increased airways reactivity, abnormal repair process, genetic factors, systemic involvement, distinctive response to infections and co-existence of co-morbid conditions[15]. This heterogeneity has motivated the emergence of multiple theories regarding the possible genesis of the disease and ultimately may provide opportunities for targeted interventions in selected patients[7].

Although controversies in COPD definition, classification, staging and screening persist, it is generally agreed that, at the population level, good quality spirometry should be widely available and extensively performed to permit an accurate estimate of the disease burden[36]. This will affect resource allocation and planning of cost-effective strategies and interventions aiming at preventing the disease and modifying its natural course. Ar-guments apart, given the unavailability of a definitive gold standard, it seems advisable to use the COPD definition proposed by GOLD since it is unambiguous, easy to re-member, reproducible in different settings and may serve as a guide to clinicians and as a standardized criterion valuable for population comparisons.

TABLE 1 - Classification of COPD severity according to GOLD criteria (based on post-broncho-dilator lung function measurements)[1]

Stage I *(Mild)*	FEV1/FVC < 0.70 FEV1 ≥ 80% of predicted*
Stage II *(Moderate)*	FEV1/FVC < 0.70 50% ≤ FEV1≥ 80% of predicted*
Stage III *(Severe)*	FEV1/FVC < 0.70 30% ≤ FEV1< 50% of predicted*
Stage IV *(Very Severe)*	FEV1/FVC < 0.70 FEV1 < 30% of predicted* or FEV1 < 50% of predicted plus chronic respiratory failure

** predicted for sex, age and height.*
FEV1 - forced expiratory volume in one second; FVC - forced vital capacity

PREVALENCE OF COPD

COPD is frequently unrecognized and a large proportion of available prevalence data probably underestimates the true burden of the disease[3,37]. In many instances, the disease becomes clinically apparent only when moderately advanced airflow obstruction is established, delaying the definite diagnosis[36]. Until recently, the interpretation of data regarding COPD burden has been impaired by the use of different methodologies to estimate its prevalence across different populations. Discrepancies in terminology, definition and diagnostic criteria, methods of identifying cases, disease coding and analytical approaches have led to conflicting prevalence estimates, with variations exceeding 15%[37]. In addition, high-quality prevalence data were largely unavailable for regions outside Europe and North America[38].

The overlap between reported respiratory symptoms, diagnosed disease and impaired lung function is variable. Symptom-based diagnosis provided the highest estimates of COPD prevalence[37]. For example, in 1979, the Mini-Finland Health Survey reported a symptom-based COPD prevalence of 22.1% in men and 7.2% in women, whilst airflow obstruction was present in 11.0% of men and 5.2% of women[39]. The inclusion of patients with chronic bronchitis but without spirometric obstruction accounted for the disagreement between estimates. Studies reporting prevalence data relying on a previous physician-diagnosed COPD provide the lowest estimates of the disease prevalence. In a semi-rural general practice in England, the overall prevalence of undiagnosed COPD was 6.2%, with 2.69 "true cases" of COPD being detected for each diagnosed case[40]. In the Third National Health and Nutrition Examination Survey (NHANES III), 24 million US adults had evidence of airflow obstruction, although, in the National Health Interview Survey, only about 10 million self-reported physician-diagnosed disease[2]. Recent epidemiological studies have adopted the criterion of airflow obstruction to provide accurate estimates of COPD prevalence. In NHANES III, the prevalence of pre-bronchodilator GOLD Stage I or higher among adults aged older than 17 years was 13.9%[41]. A population survey conducted in Spain, using post-bronchodilator spirometric data, confirmed the diagnosis of COPD in 9.1% of the population aged between 40 and 69 years[42]. The European Community Respiratory Health Survey, conducted between 1991 and 1993, reported a prevalence of 3.6% for stage I or higher COPD among young adults aged 20 to 44 years[43]. It is noticeable that, even in these studies reporting objective lung function data, the measured prevalence was highly variable. Despite having used spirometry to quantify airflow obstruction, these estimates are undoubtedly influenced by the specific lung function parameters adopted to define COPD and by distinct population demography, and comparisons should be made carefully.

Considering all the available data, definitions based on objective measurement of lung function tend to produce higher prevalence estimates than patients' self-report of a clinical diagnosis of COPD[38]. In a recently published meta-analysis, providing the first quantitative summary of COPD prevalence, whereas spirometric criteria yielded prevalence estimates of about 9-10%, a previous physician diagnosis of the disease was reported by less than 6% of subjects[38]. These numbers clearly reflect the low level of awareness of COPD, resulting in substantial underdiagnosis and underreporting of the disease. The mentioned meta-analysis observed that the pooled prevalence estimates were significantly higher in strata containing smokers, males and persons aged over 40 years. However, the authors concluded that this significant heterogeneity was incompletely explained by subgroup analysis[38].

Additional sources of variation may affect estimates of COPD prevalence, namely sampling methods, response rates, spirometry quality control and use of pre- or post-bronchodilator lung volumes to assess obstruction.

To overcome these limitations, two multinational population-based investigations, the BOLD project[44] and the PLATINO study[45], were conducted to provide more accurate and standardized estimates of country-specific COPD prevalence, appropriate for making cross-sites comparisons. Both surveys, adopting systematic quality control of spirometric data, observed a higher than previously reported prevalence of the disease in people aged 40 years and older. The overall prevalence of stage II or higher COPD reported by the BOLD initiative was 10.1% (standard error: 4.8%). In addition, a large amount of variability was observed across sites, with estimates of GOLD stage I or higher ranging between 11.4 and 26.1%. Similar data were reported in the PLATINO study, estimates of stage II or higher COPD varying between 2.6% in Mexico City and 7.1% in Montevideo. These studies showed that COPD is a greater health epidemic than has been previously realized and that differences in prevalence of COPD across sites cannot be fully explained by different patterns of exposure to known risk factors, including age and smoking.

RISK FACTORS FOR COPD

Current knowledge concerning risk factors for COPD comes mainly from cross-sectional epidemiological studies[1]. A complex interaction between genetic factors and environmental exposures has been

implicated in the development of the disease and several risk factors have been identified but a causal link is not established for all.

Smoking is recognized as the most important modifiable risk-factor causally related to development and progression of COPD[3]. Comparatively to non-smokers, smokers have an accelerated annual decline of lung function and a higher COPD mortality rate. Cumulative lifetime smoking exposure increases the risk for disease[1].

Nevertheless, not all smokers develop COPD, suggesting that genetic factors may influence subjects' individual susceptibility to disease. Smoking cessation is the single most effective intervention in COPD management because it can prevent the development of airflow obstruction or cause a marked reduction in the decline of FEV1[46] and can have a substantial impact on mortality[47]. The finding that cessation rates are far from ideal, under 30% in the best programs[48], suggests the urgent need for better tailored treatments.

There is consistent epidemiological evidence that non-smokers may develop COPD, suggesting that additional risk factors are implicated in the pathogenesis of the disease.

Age has long been recognized as a risk factor for COPD[1,49]. Across populations, the prevalence, morbidity and mortality of disease are consistently higher among the elderly[15,38,41,50]. Recently, the BOLD study reported an overall pooled adjusted odds ratio of 1.94 for stage II or higher COPD per 10-year age increment, confirming the role of age as a powerful contributing factor for COPD prevalence and possibly to disease severity[44]. In some BOLD and PLATINO countries, COPD prevalence exceeded 20% in individuals aged over 60 years[44,45]. The changing age structure of the world's population, with more people living longer due to enhanced interventions for acute cardiovascular disease and infections and, consequently, being at risk for chronic medical co-morbidities, has been claimed as one of the principal reasons for the worldwide increase in COPD prevalence[10]. Also, the effects of increasing age appear to act synergistically with those of tobacco smoking[50], further contributing to an increased prevalence of the disease among elderly smokers. Occupational exposure to several dusts, chemicals, vapours and fumes are an underappreciated risk factor for COPD[51]. An analysis of the NHANES III survey, estimated that 19.2% of COPD cases in the USA were attributable to work exposures, the proportion being higher (31.1%) in never-smokers[52]. These exposures are, in general, more important as a risk factor in low- and middle-income countries due to less stringent protective laws[15].

The role of indoor air pollution caused by exposure to biomass fuel in poorly ventilated dwellings is perfectly established as a risk factor for the development of COPD[53], being one the most important determinants of the disease, especially among women in developing countries[54]. Conversely, although outdoor air pollution is associated with increased morbidity and mortality of COPD patients[55,56], its role as a risk factor for the development of the disease remains controversial[57,58], but seems to be small when compared to cigarette smoking.

Evidence that genetic factors are involved in the pathogenesis of COPD arose from the observation of an increased risk of developing the disease among individuals with severe deficiency of alpha-1-antitrypsin[59]. COPD is a polygenic disease and several other genetic factors are sought to contribute to the individual susceptibility for its occurrence[60].

Controversy regarding gender differences in susceptibility to airflow obstruction and COPD exists[61,62] and this issue has been the topic of a great deal of research. Trends in COPD prevalence demonstrate that, in developed countries, the disease is becoming equally frequent in men and women[2], probably reflecting changing patterns of smoking habits[63]. Besides, women seem to be more predisposed to early-onset and to non-smoking-related COPD[64].

Additional potential risk factors, like lung growth, oxidative stress, respiratory infections, socioeconomic status, nutrition and asthma, although being associated with COPD, are less clearly causally related to its development[1].

At present, a comprehensive knowledge of COPD is impaired by the complexity underlying its network of causation. Further investigation that includes pre- and perinatal periods to provide a better understanding of the interactions between risk factors for disease is required. Notwithstanding, the identification of recognized modifiable risk factors is an important step toward the development of preventive strategies to reduce or minimize the burden of COPD, both at population and individual level.

NATURAL HISTORY AND PROGNOSIS

The natural history of COPD highlights that it is largely preventable and treatable, clearly illustrating that averting exposure to noxious agents would halt or at least slow lung function decline[46]. This is particularly relevant given the fact that the most important risk factor for disease is largely modifiable. In addition, recent studies suggest that interventions other than smoking cessation may alter the natural history of COPD[65].

Despite this scenario, COPD mortality rates continue to increase. According to current estimates of the World Health Organization (WHO), COPD is the fourth leading cause of death worldwide, accounting

for 3.02 million deaths, corresponding to more than 5% of the total[4]. Considering that disease-specific mortality rates are probably being underestimated due to underdiagnosis and underreporting, a higher proportion of COPD patients is dying because of the disease. In addition, COPD is frequently listed as a contributory cause of death rather than being labeled as the primary cause of death, further biasing mortality data. Moreover, the information provided by trends in COPD mortality rates over time is greatly affected by terminology and awareness[1].

In COPD patients, the relation between changing smoking patterns and disease outcomes is complex. In the US, despite the decline of smoking prevalence observed in men since the mid sixties, COPD mortality has been increasing[2]. Conversely, in developing countries that are at relatively early stages of the smoking epidemic, an increase in smoking-related COPD can be anticipated. Since COPD mortality tracks several decades behind smoking trends, an increase in mortality will probably be noticed in coming years. Contrasting with these estimates, the mortality from COPD is already decreasing in many European countries[66]. Particularly striking are the mortality trends observed in women. In Canada the death rate from COPD accelerated in the nineties and is expected to soon overtake the rate among men[67]. In US, a steep rise in COPD deaths among women has been observed since the seventies and, for the first time, in 2000, the number of women dying from COPD surpassed the number of men dying from COPD (59936 vs. 59118)[2].

The causes of death in COPD patients vary depending on the population studied[68]. Patients with mild or moderate disease usually die from cancer and from cardiovascular causes[47]. A different mortality profile emerges in patients with more severe disease, with respiratory disease being the leading cause of mortality[65]. Disease severity is usually determined based on pulmonary volumes, even though a weak correlation between airflow limitation and severity of symptoms has been demonstrated[69]. According to the ARIC study, lung function impairment is a strong predictor of mortality, with progressive airflow obstruction adversely affecting the prognosis of COPD patients[70]. However, reducing COPD to a physiologically defined disease, although being a pragmatic approach, probably does not capture the complexity and multidimensional nature of the disease. Additional predictors of survival and quality of life have been recognized and incorporated into a composite score (BODE index) able to predict subsequent mortality more accurately than any component separately[71]. This grading system uses body-mass index, airflow obstruction, dyspnoea and exercise capacity that are important components of the disease process. Emerging research suggests a potential role for several biomarkers in outcome predictions, but none of them is currently used[72].

Co-morbidities are frequently encountered in COPD patients and, in their presence, COPD can be underappreciated as a contributor to mortality. Cardiovascular disease, depression, muscle wasting, osteopenia and chronic infections often coexist with COPD, contributing to a high disease burden and to an adverse prognosis[73].

The natural history of disease illustrates that, unless interventions aiming at stopping exposures are implemented, the disease will likely progress to death[3].

COPD IN PORTUGAL

In Portugal, the burden of COPD is high. Based on the available evidence collected up to 2008, the World Health Organization estimated an age-standardized death rate for COPD of 12.5 per 100,000 in 2004, corresponding to 2700 deaths74. The Pneumobil-2 project, conducted between May 2007 and May 2008, found a prevalence of pre-bronchodilator bronchial obstruction of 30% in men and 25% in women, among 5324 smoke-exposed individuals aged 40 years or older[75]. However, reliable data regarding the true burden of COPD are lacking because population-based studies reporting the prevalence of the disease using objective measurements of lung function are not available.

Previous studies have placed Portugal at an early stage (transition between stage 2 and 3) of the smoking epidemic, the prevalence being higher in men and in more educated women[76]. This scenario is clearly in contrast with the decline in smoking habits among men observed in most European countries[63]. Considering the current worldwide estimates of COPD burden[44] and the accepted role of smoking as one of the most important causally related risk factors for the disease, it is urgent to objectively quantify COPD prevalence at a national level. Accurate estimates of the magnitude of the problem are needed to guide future planning in the definition of cost-effective preventive measures directed at discontinuing smoking epidemics. In addition, given the high rate of underdiagnosis observed in other European countries, it seems advisable to increase physician awareness for COPD and its risk factors, promoting its timely diagnosis.

CONCLUSION

Chronic obstructive pulmonary disease is a major and escalating cause of morbidity and death throu-

ghout the world, representing a substantial economic and social threat. Smoking is quantitatively the most important risk factor, highlighting that the disease is largely preventable. Less well-recognized risk factors should also be addressed because, in a large proportion of cases, they significantly contribute to the development of the disease. From a public heath perspective, the burden of the disease has been underestimated due to both the unavailability of a consensual "gold-standard" definition and underrecognition of the disease by physicians. Symptoms are nonspecific, develop late in the course of the disease and can be attributable to concurrent co-morbidities. Accurate estimates of the prevalence of the disease are needed, supporting the widespread use of good quality spirometry for diagnosis. Based on current knowledge, the prevalence of COPD is high and continues to rise in parallel with smoking epidemic. Efforts to reduce its overall burden should include preventive measures like smoking cessation and strategies aiming at stopping disease progression to modify its ominous prognosis.

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