



Adding biological markers to COPD categorisation schemes: a way towards more personalised care?

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Biomarkers may help progression from personalised to precision medicine in COPD

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Chronic obstructive pulmonary disease (COPD) is now considered as a markedly complex and heterogeneous disease [1]. Some authors even advocated that it should be called a syndrome rather than a disease [2]. Its heterogeneity is apparent in terms of clinical characteristics, natural history and prognosis, and response to treatment. It may relate to variations in the pathophysiological mechanisms involved (endotypes), which result from different complex interactions between environmental exposures (not restricted to cigarette smoke) and susceptibility genes, most of which still remain to be identified [3].

The need to personalise COPD treatment strategies

As a consequence of the disease's heterogeneity, clinicians face several challenges when caring for patients with COPD. Most importantly, they need to: 1) estimate the overall severity of the physiological deteriorations and their clinical impact, and the rate of progression of the patient's condition (disease activity) [4], which will drive the intensity of treatment and follow-up and provide insights on what can be expected in terms of evolution and prognosis; and 2) determine which therapeutic approaches will provide the best benefit/risk ratio for an acceptable cost and without upsetting patient's preferences [5]. Reaching these goals in such a heterogeneous condition requires developing categorisation systems that should ideally be: 1) accurate for the description of disease presentation and impact; 2) predictive of evolution and prognosis; 3) predictive of response to treatment; and 4) sensitive to change. Such systems are required to provide personalised medicine to patients with COPD. The disease's components that can be used to describe a patient with COPD and guide care belong to several categories termed severity, activity and impact by some authors [1], who also use the term "treatable traits" to name the patients characteristics that are accessible to treatment [6]. In the future, the management of airways diseases may move toward strategies targeting individual pheno-/endotypic features rather than historically defined diseases [7].

COPD multidimensional categorisation systems

Prognostic indexes

The number of categorisation systems used to describe COPD patients is constantly increasing, with two types of approaches: those aiming at predicting prognosis (prognostic indexes) and those aiming at grouping patients based on homogeneous combinations of features (phenotypes) [8]. Two decades ago, clinicians and researchers only used a 1-2-3-4 classification, which was mostly based on level of forced expiratory volume in 1 s (FEV₁) [9], and only two COPD phenotypes were regularly alluded to: the emphysematous and the chronic bronchitic, following the historical descriptions proposed in 1968 by BURROWS [10]. Subsequently, it

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has been clearly shown that FEV₁ cannot be viewed as sufficient to fully describe patients with COPD since it correlates only poorly with other physiological and clinical variables [11].

In 2004, *CELLI et al.* [12] proposed the BODE index (body mass index, airflow obstruction, dyspnoea, exercise capacity), which was developed to estimate the long-term prognosis of patients with COPD based on data collected at steady state. This effort was followed by several other teams, resulting in other composite prognostic indexes: BODE variations (BODEx, *etc.*), ADO (age, dyspnoea, obstruction), HADO (health, activity, dyspnoea, obstruction), DOSE (dyspnoea, obstruction, smoking and exacerbations), the COPD prognostic index. The multiplication of these tools was the consequence of a search for the best possible discriminative properties, combining high accuracy and generalisability. Indeed, comparisons of these multidimensional indices gave somewhat variable results in various populations [13–15]. Altogether, the BODE index has certainly gained the wider recognition. Importantly, studies have shown that prognostic indices may need amendments, *e.g.* recalibration, when they are applied to populations and settings other than those in which they were developed [16].

Composite prognostic indexes do not correspond to phenotypes, as there are several ways to reach a given score (except for the extreme values). Similarly, a given improvement of a score can be obtained by treating several different targets.

Phenotypes/subtypes

New ways of subtyping COPD patients have been proposed by various groups including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [17]. The 2011 GOLD categories (A-B-C-D) are based not only on FEV₁ but also on clinical components, namely dyspnoea (modified Medical Research Council grading system) and/or symptomatic impact (using the COPD Assessment Test or the Clinical COPD Questionnaire), and exacerbations (with a special mention for those requiring hospitalisations). This proposition was mostly driven by the above-mentioned observation of a rather poor relationship between FEV₁ level and the clinical impact and evolution of the disease [11]. Although not validated when first published, this classification scheme aimed at both reflecting the prognosis and guiding treatment decisions. Interestingly, the Spanish guidelines that were almost simultaneously released also proposed A-B-C-D categories, but these were established on a completely different scheme based on the presence of chronic bronchitis, emphysema or asthma on the one hand, and exacerbations on the other [18]. These are only two examples and many others exist, reflecting difficulties in approaching COPD heterogeneity and combining scientific accuracy and practical implications [19]. Such classifications aim at corresponding to clinical phenotypes as defined by patients' characteristics related to the natural history of the disease (outcomes) and/or response to treatment. However, none of these categorisation schemes has been formally shown to produce robust clinical phenotypes yet. For instance, the relationship between GOLD A-B-C-D categories and survival is variable and mortality does not systematically increase from A to D (specifically, B and C are inverted in some but not all studies) [20]. In addition, the C and D groups are quite heterogeneous in terms of future exacerbation risk, depending on whether patients join these groups through low FEV₁ only, exacerbations history only or both [21]. As a consequence, the rationale for proposing the same strategy for exacerbation prevention to patients in whom the corresponding risk is quite variable has been questioned.

To overcome the limitations of empirical classifications, attempts have been made to use mathematical methods to identify COPD phenotypes [22–25]. These approaches use descriptive multivariate techniques including factorial analyses (most frequently, principal component and multiple correspondence analyses) and clustering. Applied to cohorts of patients with COPD, these analyses allowed relatively homogeneous subgroups of patients sharing clinical and prognostic features to be identified. These results may help researchers progress in the understanding of the disease. However, so far no classification rule has been produced and validated for clinical use as a guide to care.

Room for improvement in COPD categorisation

Current categorisation systems mostly rely on clinical and lung function characteristics that are easily available in most settings. Since they cannot be considered as totally reliable to estimate prognosis or anticipate treatment response, the use of additional biomarkers has been considered, but is restricted by practicality and economic implications [26, 27]. Lung function biomarkers other than those provided by spirometry (assessing, *e.g.* hyperinflation or diffusing capacity) require additional equipment and provide results that may be less robust and more dependent on the conditions of use. Biomarkers of exercise performance also pose problems related to the skills, time and (for some tests) material required. Imaging biomarkers mainly rely on the use of computed tomography scans, which in many settings is too expensive to be implemented on a massive scale. Invasive airway sampling using bronchoscopy is obviously inadequate for routine clinical use. Sputum and exhaled air (which can be assessed using electronic nose technology) [28] can provide useful samples for research, but remain to be validated for routine use. Blood measurements could represent simple and relatively

inexpensive tools, but so far only few data are available on their potential to add value to current categorisation processes, when added to usual clinical characteristics of patients assessed at steady state.

Blood biomarkers in COPD

The main goal of initial studies on biological markers in COPD has been to improve the understanding of the pathophysiological mechanisms (endotypes) underlying COPD, its evolution and its prognosis [29]. Several types of biological variables have been studied. Many relate to inflammatory processes, others to lung proteins (club cell protein 16, surfactant protein D, *etc.*). Then it was hypothesised that biomarkers could contribute to improving care for COPD by helping to estimate the prognosis and building individualised treatment strategies. A large panel of inflammatory biomarkers was measured in 1843 patients enrolled in the ECLIPSE study, who were followed for 3 years [30]. The best clinical predictors of death during follow-up were age, hospitalisation for COPD and BODE index. The corresponding model had satisfactory predictive ability, as estimated by a *c*-statistic of 0.686. Adding serum interleukin (IL)-6 improved the *c*-statistic to 0.708. Adding nine more biomarkers (white blood cell and neutrophil cell counts, chemokine ligand 18, C-reactive protein, fibrogen, surfactant protein D, club cell protein-16, IL-8 and tumour necrosis factor- α) further increased the *c*-statistic to 0.726. Although this increase was statistically significant, the clinical relevance of the difference between *c*-statistics needs further investigation.

Regarding response to treatment, eosinophilic airways inflammation has long been known to be associated with effects of corticosteroids [31]. Importantly, blood eosinophils are more accurate to predict bronchial eosinophilic inflammation than exhaled nitric oxide fraction [32]. As such, they may represent the best routine tool currently available to identify this “treatable trait” [33]. Indeed, it was recently suggested that blood eosinophils could predict beneficial effects of inhaled corticosteroids as exacerbation preventers. Although shown in several studies [34–36], this finding only relies on *post hoc* analyses and, therefore, needs to be prospectively addressed.

Cardiovascular biomarkers in COPD

In this issue of the *European Respiratory Journal*, BOECK *et al.* [37] propose new prognostic indexes based on clinical variables (body mass index, severe exacerbations and dyspnoea) and copeptin, but not lung function. Copeptin corresponds to the C-terminal part of the vasopressin precursor and is more stable than vasopressin, which has a very short half-life compromising its use as a biomarker. It is produced by the hypothalamic–pituitary system in response to haemodynamic and osmotic stimuli. As such, it is a marker of cardiovascular stress and could be considered as belonging to a wider family of “cardiac biomarkers”. There is a strong rationale for considering such biomarkers in COPD [38]. First, cardiovascular comorbidities are frequent in these patients, resulting from common risk factors (tobacco smoking and ageing) and from the impact of COPD itself; systemic inflammation is present in 30–40% of patients [39] and COPD often leads to decreased physical activity [40]. As a result, cardiovascular diseases are more prevalent in patients with COPD than in the general population even after accounting for general demographic characteristics [41]. Secondly, COPD exacerbations are associated with an increased risk of immediate and delayed cardiovascular events. In addition, some cardiovascular biomarkers have been reported to be of prognostic value in the context of exacerbations [42]. Thirdly, cardiovascular comorbidities represent a significant cause of death at all stages of airflow obstruction [43]. The presence of cardiovascular risk factors and comorbidities is associated with poorer prognosis, with a cumulative effect with low lung function [44]. In addition, the presence of COPD impairs the prognosis of patients with major cardiovascular events, *e.g.* acute coronary syndrome [45]. Altogether, several studies found some prognostic value of cardiac biomarkers in stable or exacerbated COPD, individually or as part of a panel [46]. In a previous study, STOLZ *et al.* [47] found that adrenomedullin increases the predictive ability of the BODE index, while combining this biomarker to the BOD (body mass index, FEV₁ and dyspnoea) components of the BODE index provided better discrimination than the BODE index itself, therefore alleviating the need for a 6-min walk test. One conclusion of the study presented in this issue is that using copeptin, an easy-to-measure blood biomarker added to selected clinical characteristics, could help reliably assess the prognosis of patients with COPD in settings where lung function is not readily available, since lung function did not add to the predictive ability of the B-AE-D(-C) components (body mass index (B), severe acute exacerbations of COPD frequency (AE), modified Medical Research Council dyspnoea severity (D) and copeptin (C)). Where copeptin dosage is not available either, B-AE-D performs quite satisfactorily to predict long-term (5 years) survival, at least as well as BODE and slightly less well than ADO. Interestingly, the respective performance of the multidimensional indices of interest varied over time, with BODE score and B-AE-D(-C) indices being the best predictors of 1-year mortality while ADO and B-AE-D(-C) indices were the best for 2-year mortality. For 5-year mortality, ADO and B-AE-D(-C) indices had the best performance. All indices performed better for prediction of COPD-related rather than COPD-unrelated mortality, suggesting their “COPD-specific” character.

Conclusions

Categorising COPD is of utmost importance to provide patients with precise and personalised medicine. Categorisation mainly aims at: 1) estimating the prognosis and progression profile of the disease, which is the goal of multidimensional prognostic indexes; and 2) guiding the clinician regarding treatment choices based on the likelihood of response (and side-effects), which is the goal of pheno-/endotyping. Categorisation tools are also crucial in clinical and translational research. Most classification schemes largely used to date rely essentially on clinical and physiological variables. Adding biological markers may add to their yield. Given the diversity of available possibilities, one has to select the tool to be used considering the question that is addressed (Prognosis? Response to treatment? Research?). Additionally, when envisaging the use of biomarkers for prognosis estimation, their added value on top of clinical variables needs to be assessed and put in balance with the additional cost or complexity they induce. Current statistical methods such as the c-statistic can help in that respect, but it would be useful to determine what their “minimal clinically important difference” is.

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