



# COPD: algorithms and clinical management

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Can algorithms help the practicing clinician to prescribe the best treatment? <http://ow.ly/44yF30fwCc9>

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When you are invited to write an Editorial on a given paper, you are expected to provide a strong personal opinion that will both attract the readers' interest whilst giving food for thought. Here, we have been asked to try to achieve both goals with respect to the paper by BURGEL *et al.* [1] on the use of a simple algorithm for the identification of clinical chronic obstructive pulmonary disease (COPD) phenotypes published in this same issue of the *European Respiratory Journal* (ERJ).

As any other scientific paper, this particular one has strengths and limitations. Among the former: 1) it addresses an important clinical topic, the heterogeneity of COPD; 2) it uses novel analytical methodologies and, most importantly, it validates main observations in a second, independent cohort; and 3) it suggests a simple way to stratify COPD patients in the clinic in relation to a specific outcome (all-cause mortality). Authors merit congratulations for these three achievements. Yet, and apologies for playing the devil's advocate role here as requested, it also has some limitations that deserve comment, including: 4) what is really new for practice, beyond common clinical sense that dictates that patients with severe airflow limitation and those aged with more comorbidities (cardiovascular diseases and diabetes) have worse outcomes, and 5) how can this algorithm help the practicing clinician (and, more importantly, the patient) to prescribe the best treatment possible? Let's discuss these five points in some detail below.

## COPD heterogeneity

That COPD is heterogeneous means that not all its pathological manifestations are present in all patients at any given time point and/or at different time points in the same patient [2]. No doubt, this is an important topic with clear managerial and prognostic implications. To address it, the concept of "clinical phenotypes" was originally introduced to stratify COPD patients into groups of individuals with similar characteristics and outcomes that may therefore merit similar treatment [3, 4]. Unsupervised statistical methods, such as cluster analysis, can be used to identify clinical phenotypes in a data-driven, unbiased manner and, in fact, several studies have used them to identify key clinical features determining the heterogeneity of COPD [5–14]. Very recently, however, CASTALDI *et al.* [15] performed identical clustering analyses in 10 different cohorts in North America and Europe (n=17 146 COPD patients) and found: 1) that the reproducibility of COPD clustering subtypes across these studies was modest; and 2) that COPD heterogeneity was better characterised by continuous disease traits, coexisting in varying degrees within the same individual, rather than by mutually exclusive COPD subtypes (or phenotypes). However, it is

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important to note that, at variance with the work of CASTALDI *et al.* [15], BURGEL *et al.* [1] determined the reproducibility of their findings with respect to a specific (and important) outcome (all-cause mortality). This suggests, as highlighted by CASTALDI *et al.* [15], that “it may be useful to use differences in clinically relevant outcomes to...define...COPD subtypes”. The implication would then be that “there may be multiple distinct sets of subtypes that depend on the specific clinical outcome of interest” [15].

### Methodology and validation

BURGEL *et al.* [1] made a significant contribution to the field by using classification and regression trees to develop a machine learning-based algorithm that uses fixed thresholds for clinical variables and is able to allocate individual COPD patients to five categories related to 3-year all-cause mortality. The method was developed using the baseline characteristics of 2409 patients from the French/Belgian COPD cohorts [5] sorted into five classification categories predefined by unbiased clustering. Then, the algorithm was applied to 3651 patients of the COPD Cohorts Collaborative International Assessment (3CIA) initiative [16] proving the reproducibility of results in relation to 3 year mortality. In concordance with previous clustering results, the two groups with higher risk of mortality were older patients with cardiovascular comorbidity and diabetes, and younger patients with more severe respiratory disease [5, 13].

### Clinical implications

BURGEL *et al.* [1] showed that it is feasible to use a set of relatively simple clinical characteristics (age, body mass index, forced expiratory volume in 1 s (% predicted), modified Medical Research Council dyspnoea scale, number of exacerbations in the previous 12 months, and presence/absence of cardiovascular comorbidities and/or diabetes) to objectively stratify patients into groups of high and low mortality risk. If implemented into the clinical setting, this stratified medicine approach might be useful to define the follow-up strategy for groups of patients in order to optimise healthcare delivery and, hopefully, reduce mortality.

### What is really new?

As our grandmothers would likely say, do you really need all this complex analytical approach to know that patients with more severe airflow limitation and those with more concomitant diseases have poor prognosis? Any experienced clinician already knew it. So, in our opinion, the real value of this paper is the proof of concept that algorithms can be developed with simple clinical variables and that they can be useful for COPD stratification and risk assessment. Thus, this work reinforces the now well-accepted idea that not all COPD patients are equal and that, therefore, appropriate stratification and, eventually, individualisation of treatment [17] (see the following section) is of paramount importance.

### Individualisation of treatment

So, how do we put all this together? We believe that, at the end of the day, what really matters in practice is not to know to what group (subtype, cluster or phenotype, however you prefer to call them) the patient that you have in front of you in your office belongs but what is the best treatment that you can (should) offer to this unique individual. From this perspective, we think that the large cross-cohort analysis by CASTALDI *et al.* [15] discussed above is important, since it shows that COPD heterogeneity (if not related to a specific outcome) is better described by continuous disease traits, coexisting in varying degrees in the same patient, rather than by mutually exclusive COPD subtypes. Hence, accepting the risk of being biased, we would therefore suggest that in clinical practice, when confronted with a single patient, the concept of “treatable traits” (as discussed elsewhere in the *ERJ* [18]) is the way forward to individualise treatment, while algorithms like that developed by BURGEL *et al.* [1] can provide complementary information on the individual-patient risk in relation to specific outcomes. Treatable traits can be recognised phenotypically (observable characteristics of an organism) or through validated biomarkers that inform on the presence of specific mechanisms of disease (or endotypes) [18]. Importantly, at variance with the “phenotype” approach, they can coexist in the same individual, and change with time or as a result of treatment [18]. They can be pulmonary, extrapulmonary, and/or social, behavioural and environmental [18]. Needless to say that, as recently agreed in a European Respiratory Society research seminar on this topic, this strategy needs formal validation [19].

In any case, as requested, we have given you our personal opinion on this interesting paper by BURGEL *et al.* [1] and we hope that we might have also provided you with some food for thought. Now, it is up to you to agree or disagree. Have a nice day.

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