
COPD classification methods and informativeness on mortality: contrasting evidences

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Understanding whether the ABCD GOLD classification method is informative with respect to the spirometric classification of severity in predicting mortality of patients with chronic obstructive pulmonary disease (COPD) is subject of debate. The results of a study performed on a sample of the Norwegian population (HUNT2) were recently published. Such data showed the inferiority of ABCD classification in predicting mortality compared to the spirometric classification, which was considered the gold standard up to the 2011 version of GOLD guidelines. This result is not in line with the results of other studies that have shown the equivalence of the two classifications. The new GOLD classification seemed to be a step forward for what concerns understanding patient's needs, but it seems clear that the insertion of a single clinical variable to the spirometric data may not be exhaustive in describing all the phenomena related to a heterogeneous disease such as COPD. The publication of the HUNT study provides an opportunity to analyze how the evidence has been produced, which scientific speculations it offers, what considerations could be drawn and what further research would be appropriate.

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Chronic obstructive pulmonary disease (COPD) is a major cause of mortal-

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ity worldwide.¹ Identifying a classification method allowing physicians to properly state the risk of death is a relevant outcome in clinical research. Leivseth *et al.*² have recently published an original article reporting the results of an observational study aimed to examine the association of spirometric GOLD grades and the new ABCD groups classification³ with mortality, and to compare their statement in relation to mortality.

The authors performed a population-based study considering all residents in Nord Trondelag County in Norway from August 1995 until June 1997 aged 19 years or older. Among them, a 5% random sample and a symptom sample were invited to participate in the Lung Study.

Only participants reporting attacks of wheezing or breathlessness during the last 12 months, having ever had asthma or used asthma medication, with a post bronchodilators FEV1/FVC ratio <0.70 and those who were not included in the random cohort, were included in the North-Trondelag Health Study 2 (HUNT2) cohort, accounting for 1540 patients followed for a median follow-up of 14.6 years.

A questionnaire information concerning lifestyle, health and lung related questions was filled by participants, and all underwent a clinical examination and spirometry. Airflow limitation was graded according to GOLD criteria (GOLD1 =FEV1 $\geq 80\%$; GOLD 2 FEV1 $\geq 50 < 80$; GOLD 3: FEV1 $\geq 30 < 50$; GOLD 4: FEV1 < 30). ABCD classification was generated on the basis of symptoms burden (measured using a cut-off on "Do you become short of breath when walking on flat ground at a normal pace?" considered approximate to dyspnea grade 2 according to mMRC scale) and FEV1 or exacerbation history (generated from two questions: "Have you ever taken cortisone tablets for breathing problems/asthma?" and "How many cortisone courses have you taken in the last year"). The study cohort was followed from the date of attendance in the HUNT2 study to the date of death, emigration or end of follow up planned on May 24th, 2012. The outcome was all-cause mortality, and date of death was obtained from the Cause of Death Registry in Norway.

COPD is a heterogeneous disease with a progressive course towards a decline in lung function and, eventually, death. Why and when this occurs are still matters of debate. Thus, one of the open issues when managing COPD is to predict who is at higher risk of mortality. In other words, efforts have been made in attempting to identify those factors that may contribute to predict mortality. The 2011 GOLD classification triggered an earthquake in the respiratory community by proposing a novel assessment of severity of the disease, which combines lung function, symptoms and rate of exacerbations. This was intended as a way to emphasize the role of the physicians and

to implement the experience of the patients. The new classification into four groups (ABCD) is therefore a step forward to the needs of the patient. However, it appeared clear immediately after the release of the new document that the implications of the new classification were purely speculative. The Hunt study has the merit of comparing the spirometric (GOLD 1 to 4) with the symptom-based (ABCD) classifications in predicting mortality. The gut-feeling is that a study such as the Norwegian one should have been advocated (and awaited) before proposing the new classification. With all the limitations in mind, the conclusions of the Hunt study call for a "slow-down" when assessing the magnitude of severity on the basis of symptoms and/or exacerbations. The current study highlights the fact that an objective measurement of lung impairment is mandatory, and should not be limited. After all, spirometry remains the gold standard. Whether FEV1 is the right parameter is another story.

The HUNT study follows the previous experiences that examined the impact of the two COPD classifications on mortality.^{4, 5} In particular, Lange *et al.* (Lange P), analyzing COPD patients who were recruited from two general population studies in Denmark and followed for an average of 4.3 years, showed that both prebronchodilator spirometric GOLD grades and ABCD GOLD 2011 classification predicted mortality in general population.⁴ Which measure best predicted mortality was not formally tested in the study. Soriano *et al.*, analyzing pooled data from 11 Spanish cohorts followed for at least 10 years, showed no difference between post-bronchodilators spirometric GOLD degrees of severity and ABCD groups in predicting mortality.⁵ Data from the GenKOLS cohort of 912 patients with COPD (FEV1/FVC < 0.7 and FEV1 $< 80\%$ predicted) aged 40 to 91 years and followed for 8 years were examined.⁶ The authors state that the predictive ability of GOLD 2011 did not differ significantly from GOLD 2007 in terms of hospitalizations and mortality. The data of these studies are not in line with the results of HUNT2 study. The

HUNT study differs from the earlier studies (Agusti⁷ and Lange⁴) in evaluating the mortality according to sex. The behavior differs between females (with an apparent higher mortality in stage 3 than 4 and with an overlap between group A and B and between C and D) and males (with an overlap between stage 3 and 4 and a clear increase of mortality from group A to group D). The differences can be related to unknown factors which have not been evaluated in earlier studies.

Moreover, in groups A-D of the HUNT study, like in Soriano groups⁵ an increase of mortality from A to B to C to D, more evident in males but present also in females is reported; it seems to mean that symptoms are less important than exacerbations in determining mortality. The results are different from other earlier studies⁴ where mortality increases from A to C to B to D and were mortality increases from A to D but with an overlap in groups B and C;⁷ it seems to mean that symptoms are more or as important as exacerbations in determining mortality. Johannessen *et al.* showed that patients in GOLD 2011 group D had odds ratios of 4.1 (95% confidence interval [CI], 2.5-6.7), 9.6 (95% CI, 3.4-27), and 3 (95% CI, 0.7-13.2) relative to group A or all-cause, respiratory, and cardiovascular mortality, respectively. Associations were similar also for GOLD 2007. The adjusted AUC values for GOLD 2011 and GOLD 2007 were 0.82/0.82 for respiratory mortality (P=0.87).

Leivseth *et al.* performed the first population-based study evaluating which of the spirometric GOLD grades or the new ABCD groups is the better predictor of mortality in patients suffering from COPD. Indeed, Lange *et al.* (Lange P) evaluated a similar topic in a general population study in Denmark, but did not test which measure best predicted mortality, and Soriano *et al.*,⁵ who compared mortality according to post-bronchodilator spirometric GOLD grades and ABCD groups, did not conduct a population-based study but performed a pooled data analysis from 11 Spanish COPD cohorts. Thus, the Hunt Study mixed the features of the two previously published stud-

ies. Moreover, the association of spirometric GOLD grades and ABCD groups with mortality has been estimated by sex specific analysis, since women and men differ in many ways, including hormonal and immunological determinants, perception and reporting of symptoms, and exposure to cigarette smoke or other noxious particles and gasses.^{8,9} Notably, women showed a more severe degree of dyspnea and a worse symptom-related quality of life than man with the same level of obstruction evaluated by FEV1.⁹ Finally, all associations were adjusted for potential confounding by age, smoking and education.

Since Leivseth *et al.* included people according to lung function, both people with and without a physician diagnosis of COPD were considered. A wide age span (over 19 years old) and a wide percentage of ever smokers (ranging from 58.6% to 85.7% female and 63.4% to 78.9% male in the 4 GOLD grades of spirometric obstruction) was considered in the studied cohort. Furthermore it could be questioned, in patients with a spirometric obstructive pattern, to rule out asthma simply asking to the patients if they suffer or suffered from asthma, have or had use asthma medication and had attacks of wheezing or breathlessness in the past years. Thus, a potential bias of the study is the confusion between asthma and COPD, that cannot be ruled out merely by the evaluation of spirometry, due to the significant overlap between the two conditions.¹ The authors used a surrogate question rather than the mMRC questionnaire when assessing the symptoms burden (with a 22% of missing data on the dyspnea degree) and the participants distribution was considerably different from those presented by Lange and colleagues, while patients distribution coming from Han study, where the researchers used mMRC, were similar to those of Spanish cohort. In other word, if we need to assess the efficacy of a COPD classification method we should include only patients exactly stratified according to it.

We need more studies in different cohorts and in real life in order to explore why mortality in groups A-D seems to be

differently related to symptoms and exacerbations, phenomenon probably related to patient's phenotype and presence of comorbidities. These data allow us to better tailor the treatment (symptoms or exacerbations reduction, or, more probably, both) in order to reduce mortality.

Another important issue to consider is the impact of mortality and prognosis indexes in selecting patients undergoing lung transplantation and surgical or endoscopic lung volumes reduction. Transplant centers hardly seek survival tables to properly select the timing to propose surgical options.

All stages of COPD in the HUNT2 study² and in the ECLIPSE⁷ cohort demonstrated a five years survival higher than 60%, using both the spirometric and ABCD GOLD classifications. Such survival is similar to the post-transplantation one in COPD. These recent data confirm that, first of all, FEV1 classification is not enough to select patients undergoing lung transplantation. The data seem to confirm the first Italian survival curves study on lung transplantation, where COPD patients transplanted, selected just on the basis of lung or pump failure and FEV1 <25% predicted, survived like the ones belonging to the waiting list.¹⁰ Second, mMRC dyspnea scale and number of exacerbations do not provide much more information in predicting mortality (Group A-D) to the transplant centers. Indeed, the survival in all study groups is higher or at least similar to the lung transplant survival curves. Third, all survival curves are much better than the one in BODE cohort where the patients with FEV1 <35% (obviously not represented in GOLD studies because of the 30% cut off) had a 48 month survival of 45%.¹¹ Finally, to find a group of COPD patients with a very poor prognosis to study for lung transplantation we need to refer to Body Mass Index and 6 minute walking test, to calculate the BODE quartile. We identify, after therapy, rehabilitation and supplemented nutrition just the fourth quartile BODE index group, having a 48 month survival of 20% as optimal transplant candidate.

In conclusion COPD is a complex clinical condition where many outcomes, such

as functional, clinical and biological ones, have been evaluated during the past years. Mortality still remains a matter of debate and different studies show different results in terms of survival, in particular comparing old (stages) and new (groups) classification. Symptoms and exacerbations don't seem to add so much to the functional parameters in predicting mortality. On the other hand exercise (6 minutes walking test) and Body Mass Index integration to FEV1 seem to help the physician in evaluating the COPD patient's prognosis. Finally functional test remain pivotal in diagnosis, therapy and follow-up. What parameter, we mean with or without FEV1 could open another debate.

Riassunto

Metodi di classificazione della BPCO e informativa sulla mortalità: evidenze contrastanti

Quanto il metodo di classificazione ABCD GOLD sia informativo rispetto alla classificazione spirometrica di gravità nel predire la mortalità del paziente con broncopneumopatia cronica ostruttiva (BPCO) è oggetto di dibattito. Sono stati recentemente pubblicati i risultati di uno studio di popolazione norvegese (HUNT2) che ha evidenziato l'inferiorità della classificazione ABCD nel predire la mortalità rispetto alla classificazione spirometrica. Questo risultato non è in linea con i risultati di altri studi che hanno dimostrato l'equivalenza delle due classificazioni. La nuova classificazione GOLD era apparsa un passo in avanti per comprendere i bisogni del paziente, ma appare chiaro che l'inserimento di variabili cliniche accanto al dato spirometrico possa non essere esaustiva nel descrivere tutti i fenomeni correlati ad una patologia eterogena come la BPCO. La pubblicazione dello studio HUNT offre l'occasione di analizzare come le evidenze siano state prodotte, quali speculazioni scientifiche propongano, quali considerazioni si possano trarre e quali ulteriori ricerche sarebbero opportune.

PAROLE CHIAVE: Broncopneumopatia cronica ostruttiva - Broncopneumopatia cronica ostruttiva, epidemiologia - Polmoni, malattie.

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