

Clinical Factors Associated with an Increased Risk of Death at and During Hospitalization for an Acute Exacerbation of COPD (AECOPD) and for a Short Period after Discharge

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EDITORIAL

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide^[1]; it has been estimated that in 2030 it will become the third leading cause of death in the world^[2]. Acute exacerbations of COPD (AECOPD) are unfavourable events interrupting the stable phase of disease^[3]; an increase^[4] and specific^[5] activity of systemic inflammation and a deterioration of respiratory signs and symptoms are characteristics of AECOPD^[6].

Usually, it's common to observe and consider AECOPD as an acute event that progressively and repetitively influences the chronic natural history of COPD and causes a "loss of something"; several studies have in fact evaluated, related to AECOPD, the clinical evolution of COPD through the progressive decline in lung impairment^[7] or through the reduced quality of life^[8]. However, often COPD patients due to AECOPD require hospital admission and this aspect may have an influence on general prognosis during hospitalization and for a short period after discharge.

The close link between AECOPD and all-cause mortality was demonstrated some years ago^[9]; severe AECOPD, in fact, have been considered to have an independent negative impact on the prognosis of COPD patients^[9]. Although the frequency of AECOPD and the number of events have an important role in the mortality risk^[9], also in a long-term period of evaluation^[10], the risk of mortality does not appear to be strictly related to the level of pulmonary impairment^[11].

Clearly, the impact of AECOPD on patients is the result of the combined effects of the previous conditions of the patient, the severity of the acute event and the therapeutic decisions made by physicians. Although the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines^[13] have taught us all

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Acute exacerbations of COPD (AECOPD) are unfavourable events interrupting the stable phase of disease and that in some cases require admission to hospital; this aspect may influence the general prognosis during hospitalization and for a short period after discharge. In this editorial, we have highlighted some aspects related to the close link between AECOPD and all-cause mortality; we report several clinical factors that may be defined as risk factors for mortality at admission, during hospitalization and for a short period after discharge. These predictors of death in AECOPD may help physicians to accurately predict prognosis and therefore, behave differently in the clinical management of COPD patients.

Key words: Chronic obstructive pulmonary disease; Acute exacerbations of COPD; Hospitalization; Prognosis; Predictors

about the diagnosis and management of AECOPD^[3] and several studies published over the last decade have investigated and founded clinical factors that potentially could be determinants of mortality for hospitalized patients with AECOPD, nothing has been reported on specific and useful recommendations for patients at risk of death. In fact, the possibility of having reliable screening criteria capable of identifying early on patients at a higher risk of death in the “critical period” of hospitalization and in the early post-discharge period could be useful to physicians in the management of these patients at risk. This aspect may in fact, be true especially when defining the prognosis of patients and then, adjusting levels of care and treatments, or optimizing timing of discharge and planning a follow-up visit.

With regards to variables influencing survival and related to the general characteristics of patients, age at admission^[9,12-17], particularly in older patients^[9,13,16], has been seen to be an important indicator of poor prognosis during hospitalization^[9,12-17] and in the post-discharge period^[12,15]. Moreover, the presence of associated comorbidities to COPD^[9,12,15,17], may worsen the prognosis of AECOPD patients; in this context, cardiovascular disease plays a special role^[15,16].

Related to the severity of COPD, several factors have been defined as risk factors. In particular, it has been demonstrated that patients with chronic respiratory failure and previous need for long-term home oxygen therapy (LTOT)^[16,18] or non-invasive mechanical ventilation^[17], patients with high values at admission of dyspnoea perception^[13,15,17,18], and patients with very severe airflow obstruction (forced expiratory volume in the 1st second, FEV1 \leq 30 % of predicted)^[16,18] have an increased risk of death related to AECOPD.

With regards to clinical signs of AECOPD severity, the use of accessory inspiratory^[13,15,17] or expiratory muscles^[13], paradoxical breathing^[15,17], cyanosis^[13], lower limb oedema^[13], and impaired neurological status^[13,17], especially with a Glasgow score $<$ 15^[15] were found to be important factors related to mortality of AECOPD patients at and during hospitalization. Moreover, general blood gas alterations^[12,14,16,18-19], in particular hypercapnia^[12,14,19] or hypoxaemia^[18,19], have been found to be strong predictors of mortality. Notably, a very recent study^[12] demonstrates that the severity of respiratory acidosis in AECOPD increases progressively the risk of death during hospitalization (pH = 7.25-7.35 versus pH $>$ 7.35 Odds Ratio-OR = 1.58 with a 95% Confidence Interval-CI 1.28-1.94; pH $<$ 7.25 versus pH $>$ 7.35 OR = 2.31, 95% CI 1.72-3.10). The need for ventilatory support, moreover, increases significantly the risk of death during hospitalization (OR = 3.66, 95% CI 2.99-4.48, $p <$ 0.0001)^[12].

In the context of post-discharge mortality, early hospital readmission for a new event of AECOPD (for example, in a period within 30 days from discharge) is a variable that “per se” influences prognosis of patients. Although several variables have been found to be predictors of early readmission^[20-22], in fact, it has been demonstrated that readmission of patients to hospital in this period have a higher subsequent and progressive risk of death until in long follow-up period of 3-year^[23]. Starting from the concept that a predictor of a 30-day readmission is the variable \geq 2 previous exacerbation in a period of 1-year prior to index hospitalization (Hazard Ratio-HR = 2.47, 95% CI 1.51-4.05, $p <$ 0.001)^[23], the relationship in the events of AECOPD between the past and the prognosis is very close. Moreover, a study published in 2012 reported the presence of at least one previous exacerbation of COPD in the previous year [OR = 3.9, 95% CI 1.6-9.9, $p = 0.004$]^[19] as an independent predictor of adverse outcome defined by death during hospitalisation or the 1-month follow-up.

Finally, in order to define a specific score evaluating the prognosis of hospitalized AECOPD, an English prospective study^[24] involving more than 900 patients has found the five strongest independent predictors of death during hospitalization (extended MRC Dyspnoea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation), then combined into a clinical prediction score (DECAF, Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation). Supported by an internal bootstrap validation, the DECAF score^[24] demonstrates excellent ability in the discrimination of patient deaths during hospitalization (area under the receiver operator characteristic curve-AUC = 0.86, 95% CI 0.82 to 0.89). Moreover, in the subgroup of patients with coexistent pneumonia, DECAF exhibit a strong and significant prediction of in-hospital mortality power better than CURB-65 (Confusion, Urea, Respiratory Rate, Blood pressure, Age $>$ 65) score^[25] (AUC = 0.77 vs 0.66, $p = 0.003$)^[24].

In conclusion, several clinical factors may be defined as risk factors for mortality at admission, during hospitalization and for a short period after discharge. In this context of looking for predictors of death in AECOPD, the possibility to have specific clinical prediction tools may help physicians to accurately predict prognosis and therefore, behave differently in the clinical management of patients. Now, a very interesting question that remains to be answered is: are there any clinical factors that are potentially modifiable by specific physician intervention?

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

REFERENCES

- 1 World Health Organization, 2012. <http://www.who.int/en/> (accessed 18 Mar 2016).
- 2 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**: e442.
- 3 Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013; **187**: 347-365.
- 4 Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, Vessey RS, Wedzicha JA. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006; **174**: 867-874
- 5 Huerta A, Crisafulli E, Menéndez R, Martínez R, Soler N, Guerrero M, Montull B, Torres A. Pneumonic and nonpneumonic exacerbations of COPD: inflammatory response and clinical characteristics. *Chest* 2013; **144**: 1134-1142.
- 6 Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007; **29**: 1224-1238.
- 7 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; **57**: 847-852.
- 8 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157**: 1418-1422.
- 9 Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochoaño R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; **60**: 925-31.
- 10 Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of

- chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; **67**: 957-963.
- 11 Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011; **66**: 585-590.
 - 12 Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, Castro-Acosta A, Studnicka M, Kaiser B, Roberts CM. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016; **47**: 113-121.
 - 13 Roche N, Zureik M, Soussan D, Neukirch F, Perrotin D; Urgence BPCO (COPD Emergency) Scientific Committee. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. *Eur Respir J* 2008; **32**: 953-961.
 - 14 Groenewegen KH1, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; **124**: 459-467.
 - 15 Esteban C, Arostegui I, Garcia-Gutierrez S, Gonzalez N, Lafuente I, Bare M, Fernandez de Larrea N, Rivas F, Quintana JM; IRYSS-COPD group. A decision tree to assess short-term mortality after an emergency department visit for an exacerbation of COPD: a cohort study. *Respir Res* 2015; **16**: 151.
 - 16 Bustamante-Fermosel A, De Miguel-Yanes JM, Duffort-Falcó M, Muñoz J. Mortality-related factors after hospitalization for acute exacerbation of chronic obstructive pulmonary disease: the burden of clinical features. *Am J Emerg Med* 2007; **25**: 515-522.
 - 17 Quintana JM, Esteban C, Unzurrunzaga A, Garcia-Gutierrez S, Gonzalez N, Barrio I, Arostegui I, Lafuente I, Bare M, Fernandez-de-Larrea N, Vidal S; IRYSS-COPD group. Predictive score for mortality in patients with COPD exacerbations attending hospital emergency departments. *BMC Med* 2014; **12**: 66.
 - 18 Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; **10**: 81-89.
 - 19 Matkovic Z, Huerta A, Soler N, Domingo R, Gabarrús A, Torres A, Miravittles M. Predictors of adverse outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease. *Respiration* 2012; **84**: 17-26.
 - 20 Sharif R, Parekh TM, Pierson KS, Kuo YF, Sharma G. Predictors of Early Readmission among Patients 40 to 64 Years of Age Hospitalized for Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2014; **11**: 685-694.
 - 21 Crisafulli E, Torres A, Huerta A, Méndez R, Guerrero M, Martínez R, Liapikou A, Soler N, Sethi S, Menéndez R. C-Reactive Protein at Discharge, Diabetes Mellitus and ≥ 1 Hospitalization During Previous Year Predict Early Readmission in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *COPD* 2015; **12**: 306-314. doi: 10.3109/15412555.2014.933954
 - 22 Crisafulli E, Ortega S, Torres A. Predictors of readmission in a period of 30 days or less in acute exacerbation of chronic obstructive pulmonary disease. *Clinical Pulmonary Medicine* 2015; **22**: 172-176.
 - 23 Guerrero M, Crisafulli E, Liapikou A, Huerta A, Gabarrús A, Chetta A, Soler N, Torres A. Readmission for Acute Exacerbation within 30 Days of Discharge Is Associated with a Subsequent Progressive Increase in Mortality Risk in COPD Patients: A Long-Term Observational Study. *PLoS One* 2016 Mar 4; **11**(3): e0150737. doi: 10.1371/journal.pone.0150737.
 - 24 Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; **67**(11): 970-6.
 - 25 Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; **58**: 377-82.
- Peer reviewer:** Jeremy B Coquart, UFR STAPS, CETAPS, University of Rouen, Bd Siegfried, 76821 Mont Saint Aignan, Rouen, France.