Predictors of Long-term Mortality after Hospitalization for Severe COPD Exacerbation

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a global health problem resulting in significant morbidity. Acute exacerbation of COPD (AECOPD) is a severe complication associated with increased short- and long-term mortality. Identifying predictors of long-term mortality after a severe AECOPD may improve management and long-term outcome of this disease.

Materials and methods: A two-year prospective cohort study was undertaken in an academical medical center between 2016 and 2018. Patients with severe AECOPD who required non-invasive ventilation (NIV) were included. Baseline characteristics at inclusion, comorbidities (kidney dysfunction, left heart disease, diabetes), number of prior episodes of AECOPD and indication for long-term oxygen therapy (LTOT) or non-invasive ventilation (LTNIV) were recorded. Patients were monitored for a two-year period after initial admission. Outcomes were six-month, one-year and two-year mortality, irrespective of cause.

Outcomes: 51 patients (31 male, mean age 68.1) were included in the study. Mortality rates at six months, one year and two years were 20, 26 and 36%, respectively. Patients receiving LTOT and LTNIV at discharge had lower mortality at two years versus patients with no indication for LTOT and LTNIV at discharge. Absence of LTOT increased six-month mortality (OR .2, 95% CI, .04 to .90) and one-year mortality (p<.05). FEV1 and BMI were also correlated with long-term mortality in univariate analysis, p<.05. Age, number of prior episodes of AECOPD or the presence of comorbidities had no influence on long-term mortality.
Predictors of Mortality after COPD Exacerbation

INTRODUCTION

Every year, chronic obstructive pulmonary disease (COPD) is the main cause of death for more than three million people and also results in significant morbidity (1). Acute exacerbation of COPD (AECOPD) is a frequent complication that consists in an important aggravation of patients’ dyspnea, cough or sputum production, wheezing and chest tightness, that may either require hospitalization or at least warrant a change in medication (1). Mild to moderate exacerbations can be managed outside the hospital setting, Severe AECOPD with hypercapnic respiratory failure is a life-threatening condition which requires either invasive or, more frequently, non-invasive mechanical ventilation in an intensive care unit (ICU) or a respiratory intermediate care unit (RICU) (2). Hospitalization for AECOPD is associated with poor prognosis and increased risk of death.

Despite technical advancements in the field of mechanical ventilation and drug management, severe AECOPD is still associated with increased in-hospital and short- and long-term post-discharge mortality (3, 4). Reported in-hospital mortality rates vary between 2.5% and 30%, probably because of different patient characteristics in the different study types (4–6). For this reason, factors that predict a poor outcome are an important information to the physician, enabling him/her to decide on the proper site of care (ward, RICU, ICU), giving him/her time to adjust treatment according to the likelihood of complications, to better decide the discharge time and frequency of follow-up and also to inform the patient on the natural course of the disease (4).

In the present study, our aim was to identify predictors of mortality for up to two years after an admission for AECOPD that required non-invasive ventilation (NIV).

MATERIAL AND METHODS

An observational prospective cohort study was undertaken in a respiratory intermediate care ward in an academic medical center between 2016 and 2018. Patients who were admitted for severe COPD exacerbation and required NIV were enrolled in the study. This initial admission was considered the index point (T0) for a two-year follow-up.

During T0, NIV was started according to international guidelines criteria (7). It was applied for as long as tolerated in the first 24 hours in conjunction with standard medical treatment.
and then gradually reduced over the following days, using Trilogy A100 (Phillips Respironics, Murrysville, Pennsylvania, USA). If clinical and pH improvement could not be achieved, patients were intubated and transferred to an ICU.

Patients who had a SpO₂<88% or arterial pO₂ <55 mm Hg or pO₂<60 mm Hg and signs of cor pulmonale at rest at discharge at T0 received long-term oxygen therapy (LTOT), with an oxygen flow adjusted to maintain a SpO₂ of 88-92%. Patients with persistent dyspnea at rest (i.e., high respiratory rate >30/min) and persistent hypercapnia at discharge at T0 received long-term non-invasive ventilation (LTNIV) (ventilation mode BPAP S) with ventilation pressures adjusted for patient comfort and appropriate tidal volume (i.e., 5 mL/kg). The indication for long-term oxygen therapy and/or NIV was then assessed at each consecutive evaluation.

Patients that were successfully discharged at home were then scheduled for periodic evaluations during the next two years: first at three months and then every six months if their clinical condition remained stable or earlier if required. Patients who did not attend the scheduled appointments were monitored by phone call, or alternatively during re-admissions to our hospital. If a patient was readmitted for a new episode of AECOPD within this time frame, the follow-up interval remained unchanged.

Age, body mass index (BMI), lung function (FEV₁, FVC, and FEV₁/FVC ratio), creatinine clearance, presence of diabetes, cardiac function by echocardiography, number of admissions for AECOPD within the last year prior to T0 and length of hospital stay during the initial admission for AECOPD were recorded. Long-term oxygen therapy and NIV prescribed at discharge were also considered variables that could influence outcomes, and therefore they were also recorded.

Lung function was measured according to ATS/ERS guidelines (8) during either the initial admission (T0) or the follow-up period (during the next three months) using a microQuark spirometer (Cosmed srl, Rome, Italy). Creatinine clearance (CC) was estimated using MDRD study equation at T0 (9). A CC lower than 60 mL/min defined either acute or chronic kidney dysfunction. Presence of diabetes was defined by a prior diagnosis of diabetes and antidiabetic treatment or HbA₁c >7% and fasting glycemia >126 mg/dL at T0. Echocardiography was performed during initial admission at T0. Left heart dysfunction (LHD) was defined by at least one of the following: reduced left ventricle ejection fraction (<40%), left ventricular hypertrophy (interventricular septum and/or posterior wall thickness >10 mm), left atrium diameter >39 mm in women and >41 mm in men, moderate or severe mitral regurgitation, increased left ventricular filling pressure (restrictive or pseudo-normal trans-mitral flow pattern)

Outcomes included mortality at six months, at one year and at two years, respectively, after initial admission (T0), regardless of cause.

A statistical analysis was performed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The point-biserial correlation and Fisher’s exact test were used for univariate analysis. Where appropriate, the results were reported as correlation coefficient (r) or odds ratios (OR) with 95% confidence interval (CI). Statistical significance was considered at p<.05.

OUTCOMES

A total of 86 patients were initially included in the study following admission to our RICU with AECOPD requiring non-invasive ventilation failure during the initial episode of AECOPD was recorded in 11 patients, 10 of whom died despite intubation and mechanical ventilation, and the only one who survived was successfully discharged at home and was further included in the study. Another 25 patients were lost to follow-up because they did not attend scheduled evaluations, could not be contacted for telemonitoring

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<th>TABLE 1. Patient characteristics</th>
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<td>Length of stay (days) at T0</td>
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BMI=body mass index; FEV₁=forced expiratory volume over one second; FVC=forced vital capacity; T0=index admission; 1y-AECOPD=episodes of acute exacerbation of COPD within the last year prior to index admission T0
and had no re-admission to our hospital; they were also excluded from analysis. The final study cohort consisted of 51 patients (31 males, mean age 68.1 years). Patient flow chart accounting for all these groups of patients is shown in Figure 1, and patient characteristics are summarised in Table 1.

Ten (19%) of all patients had kidney dysfunction. Echocardiography was performed in a subgroup of 27 patients, of whom 17 (62% of subgroup patients) met our established criteria for LHD. Fourteen (27%) patients had diabetes.

After initial discharge, 39 (76%) patients received LTOT and nine (17%) LTNIV (Figure 2). Ten (20%) patients died within the first six months after T0, three (6%) died within the next six months and five (10%) died in the second year of follow-up. Mortality was 20% at six months, 26% at one year and 36% at two years.

Of the 51 discharged patients, 31 received LTOT, eight LTOT and LTNIV, and one patient received LTNIV only. Two-year mortality rates in these subgroups were 32.3%, 12.5% and 100%, respectively. Two-year mortality rate in the subgroup of patients who received neither LTOT nor LTNIV was 54% (Figure 2).

There was a statistically significant association between six-month mortality and one-year mortality and LTOT (including LTOT + LTNIV subgroup), as assessed by Fisher’s exact test, p=.04 and .03, respectively (Table 2). Of the 39 patients who received long term oxygen therapy, five (12.8%) died within the first six months of follow-up. In contrast, of the 12 patients who were initially discharged without LTOT, five (42%) died within the first six months of follow-up (Figure 3). The odds ratio of survival at six months and one year without LTOT versus...
with LTOT was .2 (95% CI, .04 to .90) and .22 (95% CI, .05 to .88), respectively.

We found no correlation of LTNIV with mortality in the whole group. However, in the subgroup of patients with LTOT after initial admission, the addition of LTNIV resulted in a significant trend towards a lower mortality at two years (12.5% versus 32.3%), but the difference was not statistically significant (p>.05).

We have also found a statistically significant positive association between BMI and one-year mortality (r=-.28) and two-year mortality (r=-.31) as well as between FEV1 and two-year mortality (r=-.35), p<.05.

The number of severe exacerbations prior to T0, age, presence of comorbidities (LHD, KD, diabetes) had no influence on long-term mortality.

### DISCUSSION

In our cohort of patients, we found a mortality rate of 20% at six months, 26% at one year and 36% at two years. While these figures confirm the well-known increased risk of death after hospitalization for severe AECOPD with NIV, the mortality rates in our study are similar but at the lower end of those reported in larger studies with rates ranging from 24% at six months up to 49% at two years (10–12). A higher incidence of death (35% after one year) is reported in patients who were admitted for AECOPD and required ICU admission for severe respiratory failure (13). All patients in our study cohort had severe respiratory failure, which was managed using NIV in our RICU and had lower mortality at one year than previously reported.

We found a lower mortality up to two years after an episode of severe AECOPD in patients with indication of LTOT (e.g., SpO2<88% or pO2<55 mm Hg at rest) as compared to patients with no such indication. This difference is most obvious in the first six months but is preserved up to two years. Current studies indicate that LTOT improves survival in stable patients with severe, but not also moderate, resting hypoxemia secondary to COPD (14); however, all these studies were done in stable patients. Also, initiation of, or ongoing, LTOT after an episode of AECOPD

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<th>Table 2: Association between recorded variables and outcome</th>
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<td>Predictors of Mortality after COPD exacerbation</td>
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Point biserial correlations except a=Fisher’s exact test; r=correlation coefficient; p=statistical significance; LTOT=long-term oxygen therapy; LTNIV=long-term non-invasive ventilation; BMI=body mass index; LOS=length of hospital-stay; FEV1=forced vital volume over one second; KD=kidney dysfunction; LHD=left heart dysfunction; 1y-AECOPD=episodes of acute exacerbation of COPD within the last year prior to index admission - T0.
has been reported to be associated with increased short-term (90-day) mortality (15) and long-term mortality (16), probably because severe hypoxemia at rest is associated with more severe forms of COPD.

Our results are somewhat different and we think this might be due to several potential causes: 1) absence of LTOT recommendation in some patients with such indication; 2) possible survival benefit of oxygen therapy immediately after a severe AECOPD even in less severe hypoxemia; and 3) associated factors/comorbidities that might influence survival. We have a protocol to prescribe LTOT at discharge according to international (BTS) and national (MoH) recommendations, and we do not think that a missed LTOT indication might be possible. However, it might be possible that some factors that improve oxygenation (oral steroids, intensive bronchodilation) are stopped after discharge, which might result in a decrease of oxygenation down to levels that require LTOT. An earlier follow-up visit (2-4 weeks) might identify this subgroup of patients and establish LTOT indication rapidly after discharge. To our knowledge, the second issue has no evidence up to now, but if noticed in several published studies, it might warrant a prospective investigation of short-term LTOT in all patients discharged after a severe AECOPD with NIV, with re-assessment of indication three to six months later.

Finally, additional factors or comorbidities might be the cause of excessive mortality in patients with no LTOT indication at discharge. We found no influence of classic comorbidities (diabetes, kidney failure, left heart dysfunction), and cor pulmonale was taken into account for LTOT indication. More subtle associated comorbidities, such as subclinical coronary artery disease, might be responsible for this finding.

Although LTNIV was not associated with a change in long-term mortality in the whole group, in the subgroup of patients on LTOT there was a clear trend that the addition of LTNIV was associated with better survival. Long-term non-invasive ventilation has been shown not only to improve survival in stable hypercapnic COPD patients (17) but also, and in association with LTOT, to reduce one-year mortality when compared to LTOT alone (18). Based on our results, we believe that addition of LTNIV in patients with LTOT indication might have a survival benefit even in those without current indication for LTNIV, and a prospective investigation of this extended indication might be warranted.

Although obesity is associated with higher all-cause mortality in the general population (19), overweight and obese patients with COPD have a lower risk of death (20). Meanwhile, underweight patients with COPD (BMI <21.75 kg/m²) is associated with a higher risk of all cause mortality (21). Our findings are in line with this data, BMI being inversely related to either one- or two-year mortality. In one study, the lowest risk of death was when a BMI at 30 kg/m² (21). Also, a BMI below 20 has been found to be associated with higher mortality rates in AECOPD patients admitted in the ICU for mechanical ventilation (22). In our cohort, mean BMI was approximately the same (29.3), which may explain the lower mortality rates.

We found FEV₁ measured during or after an episode of severe AECOPD to be negatively correlated with two-year mortality. Current published data states that a low FEV₁ or a rapid decline in lung function are each correlated with increased short- and long-term mortality (23, 24). We did not find any relation between long-term mortality and age or previous hospital admissions for AECOPD, although this relation has been described in the literature (15, 16).

Although presence of diabetes, kidney disease and cardiovascular disease has been reported to be associated with a higher risk of death in COPD patients (25, 26), such correlation was not found by us, possibly because of the low number of enrolled patients.

This study has limitations. Firstly, the final study cohort was small and therefore, the external validity of these results was probably low. Secondly, we did not use a severity index for comorbidities, so their impact on the outcomes could not be completely assessed.

CONCLUSIONS

Long-term mortality after a severe AECOPD episode that required RICU admission is lower in patients on LTOT alone and possibly even lower in patients on LTOT and LTNIV at discharge when compared to patients that had no such indication at discharge suggesting a possible
extension for these two therapeutic methods in this category of patients. A decreased lung function and a low BMI are associated with a higher risk of death on the long term. 

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