



Original Article

Prognosis Following Acute Exacerbation of COPD Treated With Non-invasive Mechanical Ventilation

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ABSTRACT

Introduction: Patients with chronic obstructive pulmonary disease (COPD) who survived an acute exacerbation with acute respiratory failure that required non-invasive mechanical ventilation (NIMV) are a group with a poor medium-term prognosis.

Objective: To identify re-admission and mortality rates within one year from discharge and to analyse factors associated with both events in a consecutive series of COPD patients treated with NIMV.

Methods: A cohort of 93 COPD patients who survived an acute exacerbation and who required NIMV was followed up after discharge. Re-admissions due to respiratory causes and survival were measured and the outcomes were analysed against possible factors associated to such events using multivariate Cox proportional risk regression analysis.

Results: Over the year following discharge, 61 patients (66%) had to be re-admitted into hospital due to respiratory complications. Upon multivariate analysis, a low FEV₁ value in stable phase and a high average length of stay were associated independently with a high risk of hospital readmission. The probability of survival at 1 year was 0.695. Age, PaCO₂ prior to initiation of NIMV and the number of hospitalisation days in the previous year were associated independently with a high mortality risk.

Conclusions: This group of COPD patients has a high mortality rate and need for re-hospitalisation in the ensuing year following discharge. The variables relating to the severity of the baseline disease and the actual exacerbation have been shown to be associated with these events, and could be applied to this subgroup of patients in specific follow-up programs.

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Pronóstico tras una agudización grave de la EPOC tratada con ventilación mecánica no invasiva

RESUMEN

Palabras clave:
EPOC
Ventilación mecánica no invasiva
Exacerbaciones
Supervivencia

Introducción: Los pacientes con EPOC que sobreviven a una exacerbación grave que necesita ventilación mecánica no invasiva son un grupo de mal pronóstico.

Objetivo: Conocer las tasas de reingreso y mortalidad durante el año siguiente a su alta y analizar los factores asociados a ambos desenlaces.

Métodos: Una cohorte de 93 pacientes con EPOC, que sobrevivieron a una exacerbación de la EPOC que precisó ventilación mecánica no invasiva, fue seguida tras el alta. Se midieron la necesidad de hospitalización

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por motivos respiratorios y la supervivencia, y se analizaron frente a posibles factores asociados a esos eventos mediante una regresión multivariante de riesgos proporcionales de Cox.

Resultados: Durante el año siguiente al alta, 61 pacientes (66%) precisaron una nueva hospitalización. En el análisis multivariante, un valor bajo de FEV₁ y una elevada estancia media durante la hospitalización se asociaron de forma independiente con un elevado riesgo de reingreso hospitalario. La probabilidad de supervivencia al año fue de 0,695 (IC 95%: 0,589-0,778). En el análisis multivariante la edad, la PaCO₂ antes de iniciar la ventilación mecánica no invasiva y los días de hospitalización en el año previo se asociaron de forma independiente con un elevado riesgo de mortalidad.

Conclusiones: Este grupo de pacientes con EPOC presenta una alta mortalidad y necesidad de rehospitalización en el año siguiente al alta. Las variables estudiadas relacionadas con la gravedad de la enfermedad de base y de la propia agudización demostraron estar asociadas a esos eventos y podrían utilizarse para la aplicación en este subgrupo de pacientes de programas específicos de seguimiento.

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Introduction

COPD is associated with periodic exacerbations,^{1,2} which can be treated on an outpatient basis, but around 4% will require hospitalisation.³ Hospitalisations are associated with an increase in mortality, in costs,⁴ and a deterioration in quality of life.⁵ The need for readmission is common, and can reach 60% in the first year after hospital discharge. Death from an exacerbation of COPD that requires hospitalisation ranges from 11-14%, reaching over 30% if mechanical ventilation is required. Exacerbations also have prognostic significance, which depends on the number and seriousness of the events.⁶

In severe exacerbations of COPD that present with respiratory acidosis, non-invasive mechanical ventilation (NIV) has shown⁷: a reduction in mortality, a reduction in the need for intubation, and a reduction in the average hospital stay. Other benefits include: faster improvement in pH, PaCO₂, PaO₂, dyspnea and respiratory rate, decreased complications, duration of mechanical ventilation and length of stay in ICU and a significant cost reduction.⁸

In terms of medium to long term prognosis, various studies^{9,10} show that in acute severe febrile respiratory acidosis, patients treated with NIV survived longer and had less need for hospital admissions. However, patients with severe COPD, chronic respiratory failure and episodes of acute or chronic respiratory failure who required acute NIMV for a severe exacerbation have a poor prognosis in the medium-term¹¹ since according to a recent study,¹² in the following year 80% of these patients had new hospitalisations for exacerbations, 63% had another severe exacerbation and 49% died.

Given the poor prognosis of these patients, it is important to develop strategies to reduce the high frequency of new hospitalisations and reduce the mortality rate. In this sense, some authors have indicated that they would consider home NIMV¹³ in this group of patients.

The aim of this work was, in a consecutive group of patients with COPD who received NIMV for a major exacerbation, survived and were discharged home, to assess the need for hospital re-admission for respiratory reasons and their survival for 12 months after discharge, identifying factors associated with both.

Methods

Environment

The centre is a tertiary-level hospital that, during the years of the study, attended a population that varied between 500,000 and 750,000 inhabitants. The hospital has 4% critical care beds, of

which half are specific units (postoperative, orthopaedic, obstetric, paediatric, etc.) and only 2% are available for intensive treatment of patients with medical conditions. It does not have a specific unit for intermediate respiratory care. In June 1994, the pulmonology department began a program of home mechanical ventilation, acquiring extensive experience with NIMV, both in acute and chronic patients. For this reason most severe exacerbations of COPD requiring treatment with NIMV are treated in the pulmonology ward. During the study period, specialised staff were not available.

Patients

Between January 2002 and December 2006 all consecutive patients admitted to the pulmonology department with severe exacerbations of COPD, treated with NIMV, and successfully discharged were included in this study. The diagnosis of COPD was made according to the GOLD¹ guidelines.

NIMV is indicated in patients with exacerbations of COPD who, after conventional treatment had a pH < 7.35 and a PaCO₂ > 45 mmHg.¹² Treatment of the exacerbation was carried out in compliance with guidelines^{1,2}: including high-dose nebulised bronchodilators, systemic steroids, antibiotics and oxygen to FiO₂ adjusted to maintain a SaO₂ level between 90 and 92%. If upon a check of arterial blood gases performed 2h after starting conventional treatment, the above criteria were sustained, NIMV was initiated. This analysis excluded patients with pneumonia, congestive heart failure, pneumothorax, and other specific causes of the exacerbation. If a patient had more than one episode of severe exacerbation with acidosis requiring NIMV during the study period, only the first of them was considered, as the index case. Later hospitalisations were recorded as one of the outcomes of the study.

The study was approved by the local ethics committee, which decided that informed consent was not necessary.

Design

Observational and prospective cohort study.

Treatment

During hospitalisation all patients received conventional treatment for COPD exacerbations based on clinical practice guidelines.^{1,2} NIMV was initiated by physicians in the pulmonology department according to a local, pre-determined protocol.

All patients who survived and were discharged were followed at visits to the pulmonology department and received the standard of care for COPD. At the time of discharge all patients were prescribed

treatment with a combination of a long acting beta 2 agonist, an inhaled corticosteroid and an inhaled anticholinergic, first ipratropium bromide, and since January 2003 with tiotropium bromide. All patients were given treatment for smoking when indicated.

A subgroup of patients who were diagnosed with sleep apnea syndrome were discharged with treatment by CPAP and another subgroup were discharged on home NIMV. In our group,^{14,15} the decision to initiate NIMV after discharge was not random and on most occasions depended on tolerance to disconnection of NIV, the level of PaCO₂, number and severity of previous admissions for exacerbation of COPD, especially previous episodes of respiratory acidosis, hypoventilation induced by oxygen; documented associated nocturnal hypoventilation, symptomatic hypercapnia, etc.

Variables

The following data were prospectively collected at baseline: demographic data (age, sex, spirometry-in the 6 previous months or after admission, Charlson's comorbidity index, total number of days hospitalised for respiratory illness in the previous year, arterial blood gases at the time of initiation of NIMV, length of stay during the initial hospitalisation and need for treatment at discharge with home oxygen therapy, CPAP and/or NIMV.

The outcomes measured were: 1) re-hospitalisations for respiratory causes in the year following, 2) death from all causes, 3) time from discharge until death. If the patient lived, the time until the last contact, and 4) the elapsed time from the first admission to the new one. If there was no new hospitalisation, the time until death or until the last contact. Mortality.

Data Analysis

Descriptive statistics: Qualitative variables are expressed by their absolute frequency distribution and percentage. Quantitative variables are described by their measures of central tendency, mean or median, together with measures of dispersion, SD or interquartile range.

Statistical Analysis

For each of two times, the time to first hospitalisation for respiratory causes and the time to death from any cause or last follow-up, the following analysis was carried out: 1) description of the time-to-event survival curves developed using the actuarial method, prognostic data are expressed as the probability of survival at one year, presented along with their confidence intervals at 95% in case survival is considered an event of death from any cause. 2) The Cox proportional hazards model was used to study the univariate association between independent variables and the "time to event". The study was completed with a multivariate Cox proportional hazards regression, in which a final model is obtained by considering those risk factors with inferior outcome at $p < 0.15$ in the univariate analysis and selection criteria by stepwise selection were used. The models were evaluated according to their predictive capability, the area under the curve was used to assess the discriminatory capacity of the models and the coefficient of determination for their performance.¹⁶ Hazard ratios were calculated for independent variables associated with the final model, and are presented together with their 95% CI. The statistical package used was: Stata version 10.1 (StataCorp, College Station, Texas.)

Results

During the study period there were 140 hospitalisations for 120 patients for exacerbation of COPD who received acute NIMV.

Only the first hospitalisation was counted for each patient, and later hospitalisations were counted as one of the outcomes of the study (need for readmission). Of the 120 patients, 93 survived to admission and all were followed after discharge. Four of these 93 patients needed tracheal intubation to overcome the ventilatory failure associated with exacerbation of COPD. Of the 93 patients, there were only four that had less than 365 days of follow-up, namely: 78, 273, 290 and 311 days. The median follow-up of the cohort was 19.4 months (IQR 7.2 to 38.0).

Table 1 shows the characteristics of the patients. According to the GOLD classification, 18 patients had very severe COPD (stage IV), 41 severe COPD (stage III) and 34 moderate COPD (stage II). The Charlson index values according to GOLD stage were: stage IV: 1.44 ± 0.73 , stage III: 1.78 ± 0.92 and stage II: 2.38 ± 1.39 . The differences between stage II and IV were significant ($p = 0.165$), but not between stage II-III and III-IV.

Upon discharge, 79 patients were discharged with home oxygen therapy; at 3 months 51% of the patients who were alive at that time maintained the therapy. Twelve patients who were diagnosed with sleep apnea-hypopnea syndrome were treated with CPAP, and 14 were discharged on treatment with NIMV. A total of 28% of patients in the series were treated with one or the other system. The group that was discharged home with NIMV had a lower FEV₁, and needed more days of NIMV before weaning (table 2). Furthermore, although not significantly, they reported more severe respiratory acidosis before starting NIMV and had required more hospitalisations for respiratory illness in the previous year.

Hospital Readmissions

During the year after discharge, 61 patients (66%) required a new admission for respiratory illness. The average hospital stay was 7 days (IQR: 0-16). The average time until the first hospitalisation was 172 days (95%: 93-236).

Figure 1 shows the curve by the actuarial method for the first hospital admission. In the univariate analysis, the factors associated with increased risk of readmission to hospital for respiratory causes were: a higher value of PaCO₂ at the time prior to initiating NIMV, a lower value of FEV₁% and a high average length of stay during hospitalisation (table 3).

In the multivariate analysis, a low value of FEV₁% ($p = 0.0008$) and a high average length of stay during hospitalisation ($p = 0.0100$) were independently associated with a high risk of readmission (table 4). The discriminating ability of the model (AUC) was 0.7601 with an R² of 0.334.

The same analysis was done excluding the 14 patients treated with home MV, and the results were very similar (table 4). The

Table 1
Patients' baseline characteristics

| | |
|--|--------------------------------|
| Age (years) | 70.7 ± 6.5 |
| Gender, M/F (%) | 83:10 |
| Charlson index | 1.91 ± 1.11 |
| FVC, L (%) (n = 85) | 1.94 ± 0.57 (62.5 ± 16.2%) |
| FEV ₁ L (%) (n = 85) | 1.06 ± 0.38 (43.4 ± 14.02%) |
| Hospital stay for exacerbation (days) | 16.04 ± 8.6 |
| Days of hospitalisation in the year previous to the exacerbation | 6.92 ± 14.6 |
| pH* | 7.24 ± 0.07 |
| PaCO ₂ * (mmHg) | 94.4 ± 21.4 |
| Home oxygen therapy at discharge | 79 (85%) |

F, female; M, male; NIMV, non-invasive mechanical ventilation.

Data expressed as average and standard deviation.

*Prior to initiation of NIMV.

Table 2
Differential characteristics of patients, as they were discharged with or without non-invasive ventilation at home (NIMV)

| | Home NIMV | No home NIMV | p |
|--|--------------|--------------|--------|
| N | 14 | 79 | |
| Age (years) | 71.3 ± 3.3 | 70.7 ± 6.9 | 0.5867 |
| FEV ₁ (L) | 0.79 ± 0.27 | 1.11 ± 0.37 | 0.0048 |
| FEV ₁ (%) | 35.7 ± 12.7 | 45.3 ± 13.8 | 0.0229 |
| pH* | 7.23 ± 0.07 | 7.24 ± 0.07 | 0.8027 |
| PaCO ₂ (mmHg)* | 106.7 ± 32.5 | 92.3 ± 18.2 | 0.1276 |
| Duration of NIMV during initial admission (days) | 14.9 ± 9.9 | 4.7 ± 5.0 | 0.0020 |
| Days of hospitalisation in the year previous to the exacerbation index | 0.93 ± 1.6 | 0.59 ± 1.2 | 0.3693 |

Data expressed as average and standard deviation.

*Prior to initiation of NIMV.

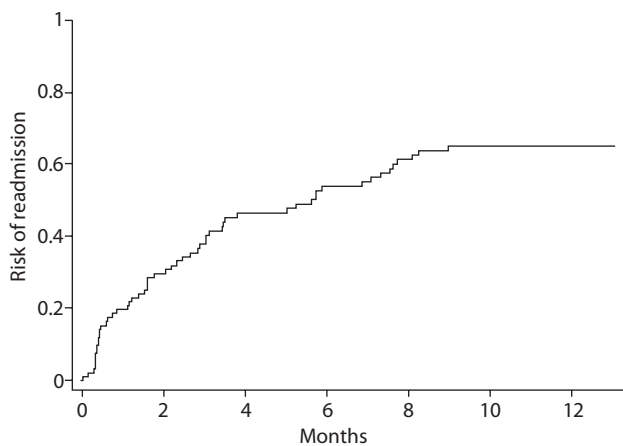


Figure 1. Curve of readmissions by the actuarial method. The figure shows, in the coordinate axis, the proportion of patients with a readmission for exacerbation of COPD, and in the horizontal axis, the time in months of follow up.

Table 3
Variables associated with readmission. Univariate analysis

| Variable | Hazard ratio (IC 95%) | p |
|--|-----------------------|--------|
| Hospital stay | 1.052 (1.021-1.083) | 0.0007 |
| Age | 1.034 (0.991-1.078) | 0.1188 |
| pH* | 0.084 (0.001-4.797) | 0.2301 |
| PaCO ₂ * | 1.020 (1.005-1.034) | 0.0074 |
| FEV ₁ % | 0.960 (0.939-0.980) | 0.0002 |
| Days of hospitalisation in the previous year | 1.014 (0.998-1.030) | 0.0771 |
| Charlson | 1.063 (0.859-1.315) | 0.5763 |
| Home oxygen therapy at discharge | 1.383 (0.626-3.056) | 0.4223 |
| Home NIMV and/or CPAP | 0.754 (0.417-1.363) | 0.3495 |
| Home NIMV | 1.649 (0.868-3.134) | 0.1266 |

NIMV indicates non-invasive mechanical ventilation.

*Prior to initiation of NIMV.

discriminating ability of the model was 0.6955 with an R² of 0.279.

Survival

The one-year survival probability (Kaplan-Meier method) was 0.69 (95% CI: 0.59 to 0.78). During follow-up (the median follow-up of this cohort was 19.4 months), mortality was 52.7%. The survival curve by the actuarial method is shown in figure 2.

In the univariate analysis, an increased mortality risk was associated with low pH and high PaCO₂ prior to initiating NIMV,

low FEV₁, advanced age, prolonged hospital stay and use of home MV treatment after discharge (table 5). In the multivariate analysis, age (p = 0.0228), PaCO₂ before the start of NIMV (p = 0.0005) and days of hospitalisation in the previous year (p < 0.0001) were independently associated with a high risk of mortality (table 6). The discriminating ability of the model (AUC) was 0.664 with an R² of 0.218.

The same analysis was done excluding the 14 patients treated with home MV, and the results were very similar (table 6). The discriminating ability of the model was 0.7717 with an R² of 0.3304.

Excluding from analysis the 12 patients for whom COPD was associated with a syndrome of sleep apnea did not change the results of the two events in the study.

Discussion

There are a few studies in literature that assess long-term prognosis in COPD patients who suffer severe exacerbations requiring NIMV. However, most of them have been published more than four years ago and refer to series studied almost 10 years ago. Recently, we have experienced significant changes in COPD management, which justify this study.

In the previous work with a greater number of patients,¹² the need for readmission and mortality at one year were 80% and 49%, respectively. In the SUPPORT study,¹¹ conducted in a population of patients with exacerbations of COPD and PaCO₂ ≥ 50 mmHg, and published before the widespread use of NIMV in COPD exacerbations, mortality one year after hospital discharge was 44%. Both studies had substantially higher mortality than those obtained in our study. In previous studies, year mortality in this subgroup of patients who received NIMV for COPD exacerbation was 16.7,¹⁰ 31,¹⁷ and 38.4%,¹⁸ which last two figures are closer to those of our study. The reduced mortality in the study of Bardi could be attributed to the small sample size: 15 patients, which may make the data unreliable.

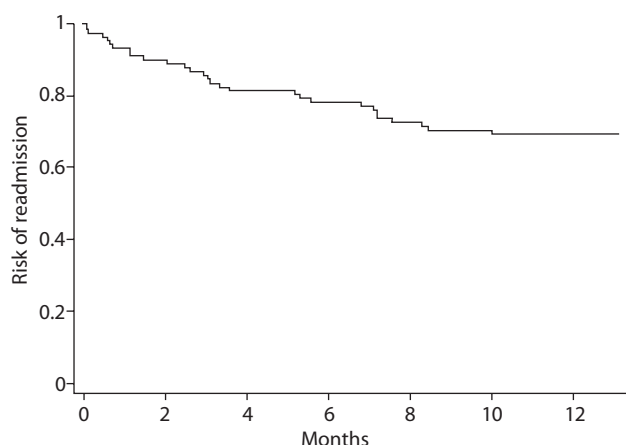
The comparison of different series of patients with severe COPD and chronic respiratory failure treated with home oxygen therapy suggests an increase in survival in the more recent series as compared with the oldest ones.¹⁹ Among the causes the introduction of new treatments such as bronchodilators, use of pulmonary rehabilitation, the decline in smoking and better management of comorbidities were mentioned. In this sense, for example, in none of the previous studies^{9-12,17,18} patients regularly receive treatment after discharge with long-acting bronchodilators with a long half-life: beta2 agonists and anticholinergics, which alone or associated with inhaled corticosteroids, have shown a reduction in the need for hospitalisation and in a recent study even a reduction in mortality.²⁰⁻²²

In our study, 14 patients (15%) were treated with NIMV after discharge. In our group^{14,15} the decision to initiate NIMV after

Table 4
Multivariate analysis of risk factors for readmission

| Variables | n = 93, includes patients with home NIMV | | n = 79, does not include patients with home NIMV | |
|--------------------|--|--------|--|--------|
| | Hazard ratio (IC 95 %) | p | Hazard ratio (IC 95 %) | p |
| Hospital stay | 1.042 (1.010-1.074) | 0.0100 | 1.068 (1.028-1.110) | 0.0007 |
| FEV ₁ % | 0.964 (0.944-0.985) | 0.0008 | 0.964 (0.941-0.988) | 0.0031 |
| | Harrell's C = 0.7601; R ² : 0.334 | | Harrell's C = 0.6955 R ² = 0.279 | |

NIMV indicates non-invasive mechanical ventilation.

**Figure 2.** Survival by the actuarial method. Survival at one year by the actuarial method in patients treated with NIMV and survived to discharge (in months).

discharge was not random and was mainly based on tolerance of disconnection of NIMV, PaCO₂ level, previous admissions, hypoventilation induced by oxygen therapy, etc. Therefore the group that was discharged with NIMV had more severe COPD (as measured by FEV₁) and many more days of NIMV during hospitalisation. Although the reality is that the published evidence does not enthusiastically support the indication of home NIMV in severe COPD,^{15,23,24} some authors propose it for the subgroup of patients with the characteristics previously mentioned.¹³ In the European study of prevalence of non-invasive home mechanical ventilation,²⁵ 36% of all patients with home ventilation in Europe in 2001 was represented by pulmonary diseases (COPD primarily, but also bronchiectasis and cystic fibrosis), and in countries such as Italy, this group exceeded 50%. Most recently in a prevalence study conducted in Valencia, COPD represented the leading cause of home NIMV.²⁶

Likewise, of the 93 patients, 12 had a confirmed diagnosis of SAHS. Since no sleep study was done for the 93 patients, it is not possible to know exactly who had obstructive sleep apnea and who did not. In the univariate analysis treatment with NIMV after discharge home and/or CPAP was not associated with readmission [0.754 (95% CI 0.417 to 1.363)] or mortality [HR: 0.951 (95% CI 0.511 to 1.768)]. Therefore it seems unlikely that the presence of these patients affected the results. Also excluding from the analysis 12 patients for whom COPD was associated with sleep apnea syndrome did not change the results of the two events in the study. Although in the multivariate analysis receiving NIMV was not associated with a reduced risk of any of the two outcomes measured, our design does not answer this question and it will come after the completion of ongoing clinical trials.

As for the factors associated with events: the need for readmission and/or mortality, only the work of Chu¹² evaluated

Table 5
Variables associated with mortality. Univariate analysis

| Variable | Hazard ratio (IC 95 %) | p |
|--|------------------------|--------|
| Hospital stay | 1.032 (1.000-1.065) | 0.0480 |
| Age | 1.100 (1.044-1.158) | 0.0003 |
| pH* | 0.018 (0.001-0.533) | 0.0202 |
| PaCO ₂ * | 1.025 (1.012-1.038) | 0.0001 |
| FEV ₁ % | 0.975 (0.954-0.996) | 0.0211 |
| Days of hospitalisation in the previous year | 1.028 (1.011-1.045) | 0.0011 |
| Charlson | 1.011 (0.799-1.279) | 0.9293 |
| Home NIMV | 0.960 (0.465-1.984) | 0.9127 |
| Home NIMV and/or CPAP | 0.951 (0.511-1.768) | 0.8731 |
| Home NIMV | 2.413 (1.250-4.660) | 0.0087 |

NIMV indicates non-invasive mechanical ventilation.

*Prior to initiation of NIMV.

these in this subgroup of patients. For the most part they referred to the severity of underlying illness (dyspnea, need for home oxygen therapy, BMI, Katz index). Similarly in our study, the average FEV₁ at admission and the average hospital stay were independent factors associated with the need for hospitalisation. Age and PaCO₂ and the need for hospitalisation in the previous year were independently associated with mortality. In a recent study,²⁷ also with a group of patients with severe COPD and discharged, 60.6% required a re-admission in the next year, which is very similar to ours, and risk factors for readmission were found to be low FEV₁, poor quality of life as measured through the St. George test of quality of life and anxiety as measured by the "Hospital anxiety and depression."

Contrary to what might be expected,^{28,29} comorbidity measured by Charlson index was neither predictive in the univariate nor multivariate analysis of mortality and/or the need for hospitalisation after discharge. This may indicate that in this subgroup of patients with very severe COPD, the prognosis is determined mostly by the respiratory disease itself. Furthermore, the comorbidity as measured by the Charlson index was significantly higher in patients with GOLD II than in GOLD IV patients, probably indicating that patients with moderate COPD exacerbations present with very serious exacerbations and that they must have associated comorbidities, especially cardiac ones.³⁰ However, it should be noted that the sample size in our study, as well as the use of just one tool to measure comorbidity—Charlson index—may limit such statements.

Our study has several limitations. Firstly, the sample size, as well as not including variables that have been associated with COPD prognosis in many studies such as BMI, dyspnea or comorbidity measured by the Charlson index. Secondly, a subgroup of patients, very significant for the sample size, was treated with NIMV or CPAP. However we do not believe that these limitations should change our conclusions. Probably this situation, together with the complexity and instability of the variables studied

Table 6
Multivariate analysis of mortality risk factors

| Variables | N = 93, includes patients with home NIMV | | N = 79, does not include patients with home NIMV | |
|--|---|----------|--|--------|
| | Hazard ratio (IC 95%) | p | Hazard ratio (IC 95%) | p |
| Age | 1.067 (1.009-1.129) | 0.0238 | 1.097 (1.030-1.168) | 0.0038 |
| PaCO ₂ * | 1.029 (1.012-1.045) | 0.0005 | 1.029 (1.010-1.047) | 0.0022 |
| Days of hospitalisation in the previous year | 1.042 (1.023-1.060) | < 0.0001 | 1.039 (1.018-1.060) | 0.002 |
| | Harrell's C = 0.664; R ² 0.218 | | Harrell's C = 0.7717; R ² = 0.3304 | |

NIMV indicates non-invasive mechanical ventilation.

*Prior to initiation of NIMV.

generate prognosis models with moderate statistical performance (R²) but with areas under the curve (0.7601, 0.664) that allow their use as predictive models to assist in decision making with such patients.

In conclusion, although patients with COPD who survived a severe exacerbation requiring the use of NIMV have a high mortality and need for readmission in the year after discharge, it is lower than in previous studies. The markers of severity of the underlying disease and the exacerbation itself are associated with increased risk of mortality and need for readmission and could be used in this subgroup of patients with specific follow-up programs.

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