Hospitalization due to exacerbation of COPD: "Real-life" outcomes

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SUMMARY

Introduction: Hospitalization due to chronic obstructive pulmonary disease exacerbation (eCOPD) may indicate worse prognosis. It is important to know the profile of hospitalized patients and their outcome of hospitalization to customize and optimize treatment.

Method: Evaluation of patients hospitalized for eCOPD, with ≥ 10 pack/years and ≥ 1 previous spirometry with airway obstruction over the course of one year at the pulmonology service of a general hospital, applying: COPD assessment test (CAT); mMRc and Visual Analogue Scale (VAS) for dyspnea; hospitalized anxiety and depression questionnaire (HAD); Divo's comorbidities and Cote index; spirometry; and laboratory tests including number of eosinophils, C-reactive protein (CRP), brain natriuretic protein (BNP). Patient progression, number of days of hospitalization and hospitalization outcomes were observed.

Results: There were 75 (12%) hospitalizations for eCOPD, with 27 readmissions, nine of which during a period ≤ 30 days after hospital discharge. The main outcomes were: number of days of hospitalization (17±16.5 [2-75]); hospital discharge (30 [62.5%] patients); discharge/rehospitalization (18 [37.5%] patients), eight of them more than once; death (7 [14.5%] patients), five during rehospitalization. We analyzed 48 patients in their first hospitalization. The sample comprised a heterogeneous group separated in three clusters according to age, FEV_1, body mass index (BMI) and CAT. The clusters did not correlate with the main outcomes.

Conclusion: Hospitalization for eCOPD is frequent. The number of readmissions was high and associated with death as an outcome. Patients hospitalized for eCOPD were a heterogeneous group separated in three clusters with different degrees of disease severity and no correlation with hospitalization outcomes.

Keywords: hospitalization for exacerbation of COPD, COPD exacerbation, COPD assessment test, Visual Analogue Scale, COPD death.

INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) in São Paulo in men and women is 14 and 18%, respectively. Its diagnosis is made by spirometry and COPD is known to be an under- or overdiagnosed disease for a number of reasons.[1,2] Episodes of more severe respiratory symptoms requiring change in routine medication used by patients with COPD are considered exacerbations of the disease (eCOPD). Hospital treatment may be necessary due to significant clinical repercussions, insufficient resources at home, failure of outpatient treatment, diagnostic uncertainty, significant comorbidities, and advanced age.[3]

Cases of eCOPD accounted for 5.8% of all respiratory hospitalizations from 1995 to 2000 in Brazil, and 12% of the patients admitted for eCOPD died.[4] Between 2000 and 2010, eCOPD was the fifth largest cause of hospitalization through the Brazilian Unified Health System of patients over 40 years of age, with approximately 200,000 admissions and annual expenditure of approximately 72 million reais.[5]

Comorbidities in patients with COPD are important in relation to the outcomes of COPD exacerbations.[6] Aging is characterized by a mild chronic inflammatory status responsible for the development of comorbidities.

More than half of patients over 65 years old have more than three comorbidities, and one-fifth have more than five.[7] There is also the development of mood disorders such as anxiety and depression. Both increase physical disability, morbidity and consumption of medical resources,[8] and can be easily assessed using the Hospital Anxiety and Depression (HAD) Scale validated in Brazil.[9]

Patients with COPD must be evaluated with objective and validated instruments, such as the mMRC scale and the Visual Analogue Scale (VAS) for breathlessness.[10] The COPD Assessment Test (CAT) is multidimensional; it includes items such as respiratory symptoms, dyspnea, daily life activity, sleep and general condition, measuring the impact of the disease on the patient's life both in periods of stability and exacerbation.[11-13]

The objective of our study was to evaluate hospitalizations for eCOPD, the profile of patients hospitalized for this condition (demographics, CAT, mMRC, VAS, HAD), duration of hospitalization, and outcomes of the hospitalizations in the pulmonology ward of a general hospital.

METHOD

We included consecutive patients hospitalized in the pulmonology ward of Hospital do Servidor Público Estadual de São Paulo (HSPE) between May/2013 and May/2014, referred from the Emergency Room, the pulmonology outpatient clinic or transferred from another service, with a diagnosis of eCOPD and at least one spirometry result prior to hospitalization showing airflow obstruction characterized by forced expiratory volume in one second over forced vital capacity (FEV_1/FVC) ratio lower than the lowest limit of normality, smoking load ≥ 10 years/pack and capable to respond to mMRC, VAS, CAT e HAD.

The data used in the analysis of the patients were only related to the first hospitalization for eCOPD in the study period. Data from readmission due to eCOPD of patients already included in the study were not considered for analysis except in cases of death.

Assessment at admission to our ward consisted of standardized anamnesis, revision of medical records, application of the mMRC, VAS, CAT and HAD scales, laboratory tests (leukometry and differential leukogram, C-reactive protein [CRP] and brain natriuretic peptide [BNP]), and radiological examinations. Clinical analyses of leukometry and differential leukogram were performed using an Advia 2120i Siemens device, whose results are reviewed within preestablished cut-off parameters: there is revision in the case of leukocytes above 13,000 and eosinophilia above 15%. Plasma CRP is measured using immunoturbidimetric assay (Beckman Coulter AU 680 and/or 5,800 analyzers) with cut-off point at 0.5 mg/dL. BNP is measured using a chemiluminescence method on a Siemens Centaur device with a cut-off point of 100 picograms (pg)/mL.

Patients received standard treatment for COPD exacerbation.[14,15] Antibiotics were prescribed after evaluation of symptoms, leukometry, CRP, and radiological and tomographic findings.

Comorbidities

After listing the comorbidities, we separated the relevant ones according to the study by Divo et al.,[6] in which 12 comorbidities showed independent risk of death:

- Oncological: Lung, pancreatic and esophageal cancer and, for women, breast cancer.
- Pulmonary fibrosis.
- Cardiac: Atrial fibrillation/flutter, congestive heart failure, coronary artery disease.
- Gastrointestinal: Duodenal/gastric ulcer, hepatic cirrhosis.
- Endocrine: Diabetic neuropathy.
- Psychiatric: Anxiety.

Then, we graded the comorbidities according to the Cote index (value ≥ 4 indicates a high probability of death):

- Breast (female), pancreatic, esophageal or lung cancer: 6 points.
- Anxiety among women: 6 points.
- Other cancers, hepatic cirrhosis, atrial fibrillation/flutter, diabetes with neuropathy, and pulmonary fibrosis: 2 points.
- Congestive heart failure, gastric/duodenal ulcer, coronary artery disease: 1 point.

The study protocol was approved by the HSPE Research Ethics Committee under No. 608,487. All participating patients read and signed the informed consent form.

Statistical analysis

Descriptive analysis of the data on hospitalization frequency, anthropometric and spirometric data, number of exacerbations in the previous year, use of O_2 at home, presence of anxiety and/or depression, mMRC, VAS and CAT results, as well as CRP, leukometry and differential leukogram[16,17] were presented as mean ± standard deviation, minimum-maximum, or number (percentage), n(%). Age, CAT, body mass index (BMI) and FEV_1 (pre-bd) were standardized to be grouped into a hierarchical cluster analysis using the Ward aggregation method and the square Euclidean distance as a measure of dissimilarity. As a decision criterion on the number of clusters to be retained, a visual inspection of the

dendogram produced was done, choosing the solution with the lowest number of clusters. The classification of the retained clusters was later refined through a non-hierarchical K-means procedure. One-way ANOVA was used to compare the variables that formed the clusters. The association between categories and clusters that were formed was performed using Pearson's Chi-square and Fisher's exact test if necessary. The Kruskal-Wallis test was performed to identify differences in the quantitative variables among the clusters. All analyzes were performed in SPSS statistics v.21 software, adopting a significance level of p<0.05.

RESULTS

During the study period, there were 639 hospitalizations in the pulmonology ward, of which 102 were initially diagnosed as eCOPD, according to the International Code of Diseases (ICD), while 537 received other diagnoses. Of the 102 patients, 57 patients were excluded: 19 did not have diagnostic confirmation of COPD, and 38 did not meet the inclusion criteria. Of the 537 patients initially admitted with other ICD codes, 30 ultimately had a diagnosis of exacerbation of COPD, i.e., there were 75 (12%) admissions for COPD (Figure 1), of which 27 were readmissions – 18 patients returned once and eight more than once, and of the total number of readmissions, nine were

early readmissions (less than 30 days after last hospital discharge for eCOPD) – and 48 were first-time admissions.

The sample was composed of the 48 patients admitted for the first time, who underwent anthropometric data verification and application of objective tests to assess dyspnea, symptoms (CAT), anxiety and depression, and laboratory parameters.

The duration of the first stay of each patient in the study period was 17±16.5 (2-75) days. The outcomes of the 75 hospitalizations for eCOPD were: 28 (37%) for hospital discharge, 27 (36%) for discharge + readmission, and seven (9%) deaths. Of the seven deaths, five occurred in readmissions.

Table 1 shows that half of the individuals were male; 90% were white; the mean age was 73.5±7.37 (51-94) years; smoking amounted to 44±29 (10-155) pack-years; 37 (77%) were former smokers; 20 (42%) reported exposure to wood stoves; 8 (17%) had had bronchitis in childhood; 33 (69%) had ≥ 2 exacerbations in the previous year; mean follow-up time with a pulmonologist was 6±5 (0.5-17) years; the number of spirometries per patient prior to admission was 3±2 (1-9); pre-bd FEV_1 was 1.1±0.4 (0.4-2.1) L and 44%±17% (16-79) of the predicted value; 40 (92%) of the patients had a post-bd FEV_1 of 1.1±0.4 (0.5-2.2) L and 46%±17% (25-88) of the predicted, and 22 (46%) were oxygen dependent.
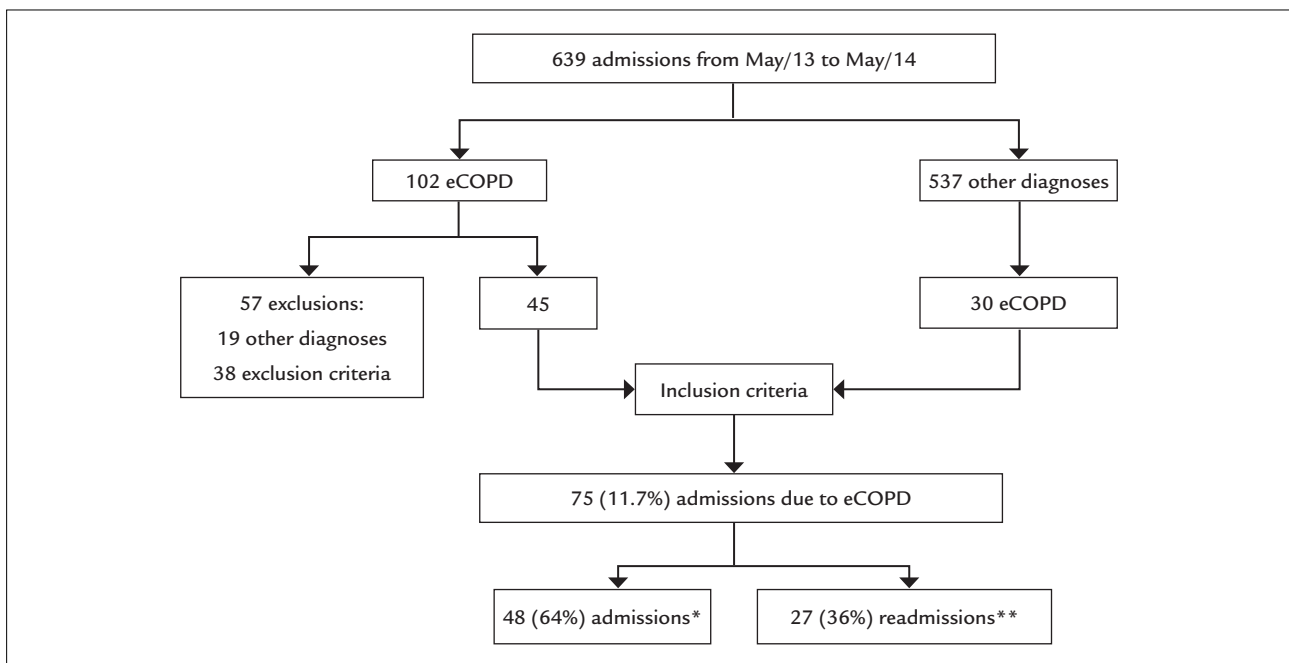
FIGURE 1 Flowchart study.

*First admission in the study period
**18 (37.5%) patients readmitted, 8 more than once, with a total of 27 readmissions, 9 early (≤ 30 days).
30 (62.5%) hospital discharges
7 deaths { 5 deaths ocurred in readmissions
{ 2 deaths in the first admission

TABLE 1 Characteristics of the 48 patients.

Results as n (%) or ± SD (min-max):

Male	24	50%
White	43	90%
Age	73±7.4	(51-94 years)
BMI	26±7	(15-56)
Years-pack	44±29	(10-155)
Former smokers	37	77%
Exposure to wood stoves	20	42%
Bronchitis in childhood	8	17%
≥ 2 exacerbations in the previous year	33	69%
n. of comorbidities in 48 (100%)*	4.2±2.2	(1-9)
Divo classification in 24 (50%)	0.8±0.9	(0-3)
COTE index in 22 (46%)	1.9±2.6	(0-8)
COTE index ≥ 4	10	21%
Time of FUP	6.2±4.6	(0.5-17)
n. of spirometries/patient	3±2.1	(1-9)
FEV_1, pre-bd L	1.1±0.4	(0.4-2.1)
% predicted FEV_1, pre	44±17	(16-79)
FEV_1/FVC, pre	48±10	(27-69)
FEV_1, post-bd L**	1.1±0.4	(0.5-2.2)
% FEV_1, post**	46±17	(15-88)
FEV_1/FVC, post**	47±09	(23-65)
Home O_2 therapy	22	46%

BMI: body mass index (kg/m²); FEV_1, pre or post: forced expiratory volume in one second, performed before or following bronchodilator administration; % predicted: percentage of the predicted value according to age and height; FVC: forced vital capacity; FUP: follow-up with a pulmonologist.
*High blood pressure,, cardiovascular diseases, DM, dyslipidemia, hypothyroidism, rheumatic diseases, liver disease, non-dialytic renal insufficiency, cancer, osteoporosis, gastrointestinal diseases.
**40 patients.

The number of comorbidities found in 48 patients was 4.2±2.2 (1-9): high blood pressure, cardiovascular disease, diabetes mellitus, dyslipidemia, hypothyroidism, rheumatic diseases, liver diseases, non-dialytic kidney failure, cancer, osteoporosis and gastrointestinal diseases. According to the criteria by Divo,[6] 24 (50%) had comorbidities that increased the risk of death. Ten patients (21%) had Cote score ≥ 4, of whom two died.

The causes for the seven deaths were: respiratory failure in four patients who had advanced COPD and used O_2 at home, and cancer in three patients (lung, breast and undetermined primary site carcinomatosis).

The results of the dyspnea, CAT and HAD scales were: high/very high impact of exacerbation in the patient's life according to CAT in 25 (50%) patients, moderate impact in 15 (33%), and low impact in five (11%); degree of dyspnea from 0 (poor) to 100 (optimal) mm according to VAS at 48±29 (4-100) mm; and mMRC at 3±1 (1-4).

Anxiety was present in 15 (31%), depression in 17 (35%) and anxiety plus depression in seven (14.5%). Regarding laboratory tests at admission, CRP was increased in 38 (89%) patients; there was leukocytosis (leukocytes > 10,000) in 30 (62.5%); eosinophilia > 2% in eight (17%); and BNP > 100 in 16 (39%), ranging from 303±201 (112-809).

Age, FEV_1, BMI and CAT were variables correlated with disease severity and grouped for cluster analysis. This analysis was performed with 45 valid measures of CAT, age, pre-bd FEV_1 and BMI, whose values, in addition to the Z score, discriminated three clusters with p<0.05. The square Euclidean distances between patients generated a dendogram, with three clusters on visual inspection. The classification of each individual in the three clusters was refined with the "K-means" method and is shown in Figure 2.
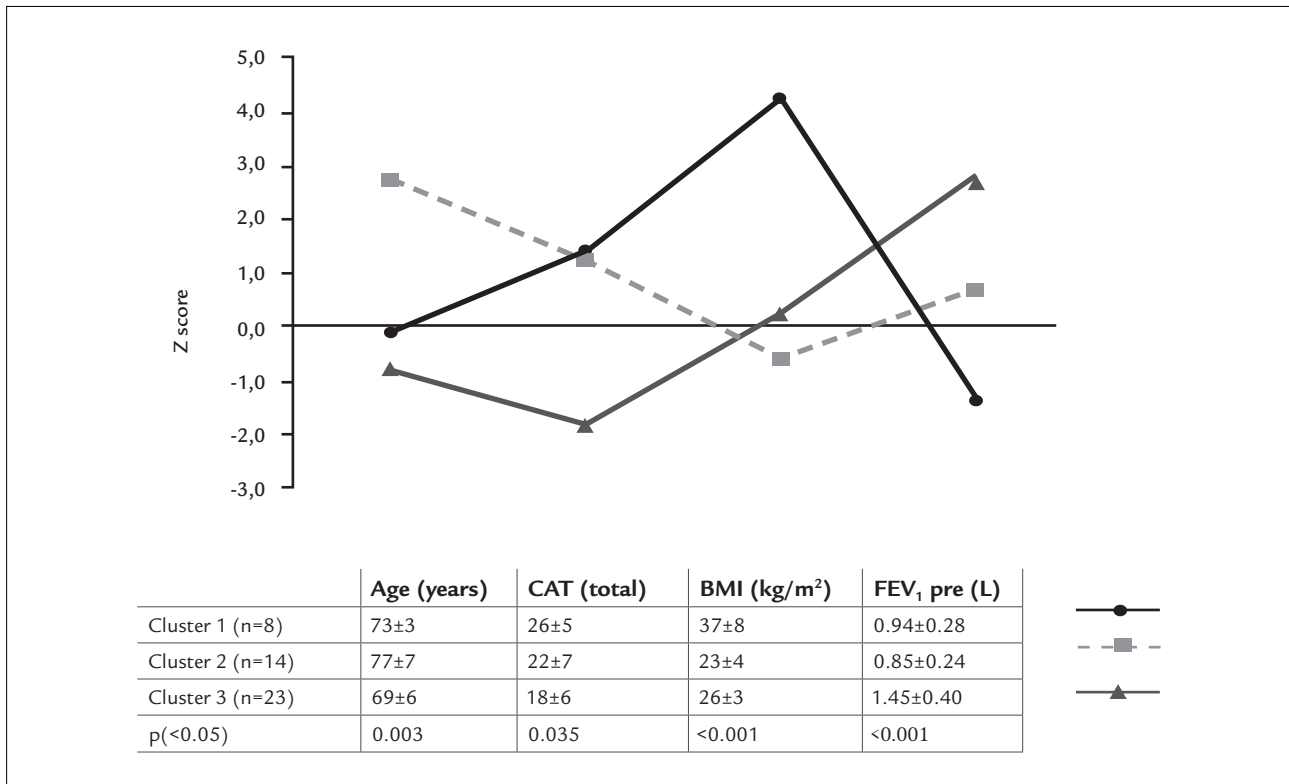
- Cluster no. 1 had eight (16.7%) patients, 75% female and 25% male with age close to the mean, higher CAT and BMI results, and lower FEV_1.
- Cluster no. 2 included 14 (31%) patients, who were older and had higher CAT results, BMI within normal range and also lower FEV_1.
- Cluster no. 3 had 23 (51%) patients who were younger than the average, with a lower CAT score, BMI compatible with overweight and higher values for FEV_1.

The hospitalization outcomes (discharge, readmission and death) and other characteristics of the sample, except for mMRC, did not present a statistically significant difference between the clusters. The mMRC presented a statistically significant difference among the clusters (p=0.001).

All patients with the exception of three had eCOPD due to infection. Antibiotics were prescribed for 45 (94%) of the patients, of whom 34 (75.5%) progressed well. However, 11 (24.4%) patients had an unfavorable outcome and there was a need for initial antibiotic therapy replacement. Tuberculosis was diagnosed in one of the patients in the study sample.

Discussion

Admissions in the pulmonology ward of HSPE due to eCOPD accounted for 12% of the total number of admissions from May/2013 to May/2014. The rate of COPD underdiagnosis was 5% (30/537), while overdiagnosis occurred in 18% (19/102). The rate of COPD underdiagnosis in São Paulo is 14%.[1] In the US, this rate reaches 50%, and occurs due to several factors such as lack of knowledge about COPD or lack of suspicion for its diagnosis, which often occurs during the exacerbation.[18,19]

	Age (years)	CAT (total)	BMI (kg/m²)	FEV₁ pre (L)
Cluster 1 (n=8)	73±3	26±5	37±8	0.94±0.28
Cluster 2 (n=14)	77±7	22±7	23±4	0.85±0.24
Cluster 3 (n=23)	69±6	18±6	26±3	1.45±0.40
p(<0.05)	0.003	0.035	<0.001	<0.001

FIGURE 2 Standardized variables related to disease severity (age, CAT, FEV₁ and BMI) allowed grouping of patients into three clusters.

Table 1 shows that patients have a high average age and that in some the follow-up period with a pulmonologist was only 6 months, that is, the diagnosis was recent, and as a consequence, the number of spirometries performed was small. It is interesting to note that several patients (38) were not included in the study because they had never undergone spirometry (inclusion criteria), a fundamental exam for the diagnosis of COPD.[18] COPD underdiagnosis results in late recognition of the disease and in later stages.[19,20] Early detection of airflow limitation and smoking cessation intervention may delay the decline of lung function, reduce COPD symptoms, and improve the patient's quality of life.

In a retrospective study of COPD patients hospitalized for respiratory failure over a period of 8 years, only 31% had a diagnosis confirmed by spirometry despite having a clinical diagnosis of eCOPD,[19] which characterizes overdiagnosis.

Patients with a smoking load ≥ 10 packs/year were included in this study. Smoking is the most frequent cause of COPD, although there are other risk factors such as exposure to occupational dust, air pollution and biomass burning.[20] We observed that 42% of our patients reported exposure to wood stoves.

Still in relation to the characteristics of the sample, 17% of the patients had a history of bronchitis in childhood. It is known that the prevalence of asthmatics who smoke is similar to that of the general population, and that many COPD patients may present a history of asthma prior to COPD. COPD is often confused with asthma.[21,22] The coexistence of these conditions is called asma-COPD overlap syndrome.[23] With increasing age, there is an increase in the proportion of patients with this syndrome. Some studies found that 55% of COPD patients over 50 years of age had asthma, whereas in other studies the prevalence of asthma-COPD overlap syndrome ranged from 13 to 19%.[23]

Patients hospitalized with eCOPD had 4.2±2.2 comorbidities, which is consistent with reports in the medical literature that these are more frequent in patients with COPD than in the general population.[24] Some comorbidities present in patients with COPD affect the prognosis, as described by Divo and Cote.[6] In our study, the Cote score was higher than 4 for ten patients (21%), which means an increased risk of death. There is evidence that the specific management of COPD reduces the number of exacerbations leading to clinical stability for comorbidities with reduced mortality. The same happens with the treatment of comorbidities, which affects the stability of COPD.[24,25]

Management of COPD aims to control symptoms and comorbidities, and prevent exacerbations.[3] Hospitalization due to eCOPD does not necessarily occur in patients with more advanced disease[26] and, in our study, we found that the patients had different grades of severity, despite the fact that FEV_1 pre-bd was 44%±17%, and 22 (45%) patients used oxygen at home.

Mortality in eCOPD is high and we observed in our study frequent readmissions that correlated with the outcome of death, as described by Hurst,[27] Soriano,[28] and Teixeira,[29] the latter in Brazil. Teixeira says that 87.8% of the patients hospitalized with COPD had two or more comorbidities, and hospital mortality due to eCOPD was 37.7%.

The length of hospital stay was 18±17 days. We observed the heterogeneity of clinical manifestations in COPD patients through CAT variability and dyspnea as measured by mMRC and VAS.[30] There is a correlation between high CAT score and higher frequency of exacerbations, reflecting both severity and duration. CAT may assist in assessing the severity of the exacerbation.[12,31]

The prevalence of depression found in the sample was 35%. Coexistence of anxiety and/or depression with COPD increases the number of exacerbations and hospitalizations.[8,32]

Biomarkers are useful to monitor patients admitted with eCOPD. The presence of eosinophilia > 2% indicates a better response to steroid therapy,[16] and it was found in 20% of the patients. CRP and BNP are useful biomarkers for monitoring, respectively, infectious exacerbations and cardiopathies.[17,26,33]

The seven deaths reported in our study were due to respiratory failure (four patients) and cancer (three patients). Respiratory failure correlates with more severe COPD, whereas lung cancer affects 9% of COPD patients, regardless of staging.[28]

The standardized analysis of age, CAT, FEV_1 and BMI allowed grouping of patients into three clusters (Figure 2), with different degrees of severity and no correlation with the outcomes of hospitalization. In the first group there were more women with lower FEV_1, higher BMI, and CAT displaying high scores. In the second group, there were older patients with high CAT; and in the third group, younger patients, with higher FEV_1 and lower CAT scores, which indicates less severe COPD in this group with a greater number of patients.[34]

Readmissions due to eCOPD are a marker of poor prognosis. The number of readmissions was high in our study, which points to the need to adopt protocols for hospital discharge and appointment scheduling soon after discharge, with referral to a pulmonary rehabilitation program.[35]

The small number of patients included in the sample was a limitation in our study, and was due to a high rate of readmissions and failure to meet the inclusion criteria.

COPD exacerbation is an event that often requires hospitalization and progresses with a high mortality rate. Many times, COPD is under- or overdiagnosed, and one reason is underutilization of spirometry. Thorough assessment of these patients on admission, using laboratory tests, comorbidities assessment, and objective instruments to quantify dyspnea and symptoms (mMRC, VAS and CAT) is essential to reduce hospital stay, prevent readmission and decrease mortality.[36,37]

Patients admitted due to eCOPD are a heterogeneous group that can be grouped into three clusters as described, although we did not find an association between these clusters and the outcomes of hospitalization. Studies with a larger sample of patients are needed to confirm the findings reported here and to relate them to the outcomes of hospitalizations due to eCOPD.

Resumo

Hospitalização por exacerbação da DPOC: desfechos da "vida real"

Introdução: As hospitalizações por exacerbação da doença pulmonar obstrutiva crônica (eDPOC) podem indicar um pior prognóstico. É importante conhecer o perfil dos pacientes internados e os desfechos das internações para personalizar e otimizar seu tratamento.

Método: Avaliação dos pacientes hospitalizados por eDPOC, com ≥ 10 anos/maços e ≥ 1 espirometria prévia com obstrução ao fluxo aéreo no período de um ano em um serviço de pneumologia de um hospital geral. Foram utilizados: teste de avaliação da DPOC (CAT); mMRC e Escala Analógica Visual (EAV) para aferição da dispneia; escala hospitalar de ansiedade e depressão (HAD); comorbidades pelos critérios de Divo e índice de Cote; espirometria; e exames laboratoriais, eosinófilos no sangue, proteína C reativa (PCR), brain natriuretic peptide (BNP). Observamos evolução dos pacientes, duração da internação e desfechos da hospitalização.

Resultados: Ocorreram 75 (12%) internações por eDPOC, sendo 27 reinternações, nove das quais com menos de 30 dias após a alta. Os principais desfechos foram: duração da internação de 17±16,5 (2-75) dias; 30 (62,5%) altas hospitalares; 18 (37,5%) altas/reinternações, oito pacientes reinternaram mais de uma vez; e sete (14,5%) óbitos, cinco durante as reinternações. Analisamos 48 pacientes em sua primeira internação. A amostra era um grupo heterogêneo

que ordenamos em três *clusters* de acordo com idade, VEF_1, índice de massa corporal (IMC) e CAT. Os *clusters* não se correlacionaram com os principais desfechos.

Conclusão: A eDPOC é causa frequente de internações. Foram frequentes as reinternações e estas se correlacionaram com o desfecho óbito. Os pacientes internados por eDPOC formaram um grupo heterogêneo, que pôde ser agrupado em três *clusters* com diferentes graus de gravidade e sem correlação com os desfechos das hospitalizações.

Palavras-chave: hospitalização por exacerbação da DPOC, exacerbação da DPOC, teste de avaliação da DPOC, Escala Analógica Visual, morte por DPOC.

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