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Factors associated with the rate of COPD exacerbations that require hospitalization

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Background/aim: Exacerbations are key events in chronic obstructive pulmonary disease (COPD). Frequent exacerbations occurring during the natural course of COPD lead to deterioration of health-related quality of life and are major causes of morbidity and mortality. The aim of this study was to identify factors independently associated with frequent severe exacerbations of COPD that require hospitalization.

Materials and methods: A case-control study was performed to analyze risk factors and frequency of severe exacerbations, which were defined by the GOLD guideline criteria. Stepwise multivariate regression was used to determine the significant predictors of frequent exacerbations.

Results: Results revealed five independent predictors of frequent exacerbations: age, length of hospital stay, FEV1/FVC ratio, CRP level above 10 mg/L, and respiratory comorbidities.

Conclusion: COPD patients should be more carefully assessed in terms of age, length of hospital stay, FEV1/FVC ratio, CRP level, and respiratory comorbidities. Patients under 65 years of age with respiratory comorbidities, longer hospital stay, lower FEV1/FVC ratio and CRP of <10 mg/L are more prone to experiencing a minimum of one additional hospitalization in the following year. Patients could spend less time in the hospital environment and increase their quality of life by adjusting these risk factors for hospitalization due to COPD.

Key words: Chronic obstructive pulmonary disease, severe exacerbation, exacerbation frequency, risk factors, hospitalization

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a both treatable and preventable clinically heterogeneous syndrome, with prevalence somewhat lower than 6% (1). Frequent exacerbations occurring during the natural course of COPD lead to deterioration of health-related quality of life and are major causes of morbidity and mortality (2). They have high prevalence and high impact on disease progression and prognosis; they accelerate the decline in lung function, have a negative impact on quality of life, promote frequent clinic visits and hospitalizations, and are responsible for a large proportion of the health care costs (3–5).

Recently, a distinct subgroup of patients named "frequent exacerbators" was introduced (2,3). These are the patients with comparable lung function impairment to that of other patients, but with more frequent exacerbations. Although this frequent exacerbator phenotype occurs regardless of GOLD stage, the exacerbation rate increases with severity of the disease (3–8).

To date, the history of exacerbations has been recognized as the single best predictor of future events (3,9). Obvious correlation has been revealed between decreased lung function and disease severity (10), elevated white-cell count (3,11), hematocrit level of <41% (12), BODE score, sex, age, smoking status, body mass index, presence of cardiovascular comorbidity (13,14), influenza and 23-valent pneumococcal immunizations (5), and frequency of severe exacerbations of COPD. However, other studies failed to confirm the influence of other risk factors such as blood glucose level, FEV1% predicted, long-acting bronchodilator use, or inhaled or systemic steroid use (2,15).

Prevention of exacerbations is a key component of strategies for COPD treatment and that is why it is important to understand the risk factors, incidence, characteristics, and effects of exacerbations in patients with COPD. Nevertheless, it is important to identify patients at risk for frequent exacerbations at various levels of disease

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severity (16). The aim of this study was to identify factors associated with frequent severe exacerbations of COPD that require hospitalization.

2. Materials and methods

2.1. Study subjects

In this retrospective case-control study we examined the risk factors and frequency of severe exacerbations in COPD patients that were hospitalized due to index exacerbation of COPD in the tertiary care university hospital Clinical Center of Kragujevac during a 3-year period (2010–2012). A total of 512 individual medical records were reviewed representing all hospitalized patients with COPD during the study period. We analyzed both female and male patients above 18 years old with established diagnosis of COPD, and 174 patients fulfilled these criteria and were included in further analysis. A group of 64 subjects who were frequent exacerbators formed the study population while 110 patients were in the control group. The remaining patients were excluded from the study due to incomplete patient files and several conditions that reduce lung function: associated restrictive disorders (interstitial fibrosis, tuberculosis, etc.), a history of lung cancer, previous lung surgery, recent myocardial infarction, or pulmonary embolism, as described elsewhere (2). For the purposes of this study, respiratory comorbidities were defined as acute or chronic, partial or global respiratory failure.

The study protocol was approved by the ethical board of the Clinical Center of Kragujevac.

2.2. COPD exacerbations

COPD exacerbation was defined by the criteria of the GOLD guidelines (1). We analyzed only severe exacerbations that required hospitalization.

2.3. Statistical analysis

Baseline demographic characteristics of the patients were described by means ± SD for continuous variables and frequency (percentages) for categorical variables. In order to determine differences in the mean values of continuous variables with normal distribution of values, the parametric Student t-test was used, and its nonparametric alternative, the Mann–Whitney test, was used if data did not follow a normal distribution. Differences between groups in the incidence of certain categories were determined by chi-square test or the Fisher test of real likelihood for low frequencies. Potential predictors of the observed outcome were determined using binary logistic regression, and values of the crude and adjusted odds ratios with corresponding confidence intervals of 95% were used to express the strength of correlations. All data were analyzed using SPSS 20 where $P < 0.05$ was considered statistically significant.

3. Results

This case-control study was conducted on 174 patients divided into two groups. The difference in age and mean level of BMI between the groups was statistically significant ($P = 0.005$, $P = 0.018$). Patients who had at least two exacerbations during the study period stayed longer in the hospital ($P = 0.001$) and had lower values of lung function parameters (FEV1 predicted %, FEV1/FVC ratio: $P < 0.001$, $P = 0.001$). A value of FEV1 of <50% was also more often noted in the group of frequent exacerbators ($P = 0.007$). Respiratory comorbidity rates were different between the groups ($P = 0.014$). Furthermore, patients in the control group had higher serum levels of CRP ($P = 0.005$) and higher frequency of CRP level above 10 mg/L ($P = 0.012$). We also found differences in the erythrocyte count ($P = 0.008$) and the rate of prescribing preventive therapy ($P = 0.047$). Baseline demographic characteristics of the patients are shown in Table 1.

These baseline assessments were used as a starting point to analyze factors associated with frequent exacerbators. The best potential predictors of future exacerbations were age, length of hospital stay, FEV1 level, FEV1 <50%, FVC, FEV1/FVC ratio, respiratory comorbidities, frequency of CRP level above 10 mg/L, number of erythrocytes, and percentage of prescribed preventive therapy. Other results of univariate logistic regression are shown in Table 2.

Factors that were associated with frequent exacerbators were assessed by a stepwise multivariate regression model. Results of this analysis revealed five independent predictors of frequent exacerbations: age, length of hospital stay, FEV1/FVC ratio, CRP level above 10 mg/L, and respiratory comorbidities (Table 3).

4. Discussion

The results from our study have shown that the patients under 65 years with the presence of respiratory comorbidities, longer hospital stay, lower FEV1/FVC ratio, and CRP <10 mg/L are more prone to experience a minimum of one additional hospitalization in the following year. Several studies have shown the association of a range of variables with frequency of different COPD exacerbations (3–14).

We have noticed that age is associated with future exacerbations. Interestingly, it seems that older patients are less prone to experiencing at least two exacerbations in a year, which is inconsistent with a number of previous reports. Some studies failed to explain the influence of age on COPD exacerbations. Previous data showed that an increase in age of 10 years could produce about 3.5% increase in exacerbation rate in the following year (17). Older patients (11,18) and the patients above 65 years of age also had greater risk for repeated hospitalizations (19,20). Reexacerbation in 90 days was shown to be associated with

Table 1. Baseline characteristics of the patients.

Variables	Cases (n = 64)	Controls (n = 110)	Test	P-value
Age, years	64.9 ± 10.8	68.9 ± 8.6	Z = –2.814	0.005
Sex, male (%)	67.2 (n = 43)	68.2 (n = 75)	χ^2 = 0.018	0.892
BMI, kg/m^2 [a]	26.8 ± 6.3	24.2 ± 5.7	Z = –2.369	0.018
Current smoker (%)	48.4 (n = 31)	52.7 (n = 58)	χ^2 = 0.298	0.585
Smoking (pack-years)	36.7 ± 26.1	36.5 ± 25.4	Z = –0.298	0.766
LOH stay [b]	15.1 ± 6.4	11.9 ± 4.4	Z = –3.192	0.001
FEV1, predicted (%) [c]	36.5 ± 14.3	45.4 ± 15.5	Z = –3.659	<0.001
FEV1 <50% (%) [c]	82.8 (n = 53)	63.6 (n = 70)	χ^2 = 7.181	0.007
FVC	80.4 ± 21.1	88.5 ± 22.2	T = 2.259	0.025
FEV1/FVC ratio, (%) [c]	45.1 ± 9.9	51.1 ± 10.6	Z = –3.224	0.001
Comorbidities (%)	92.2 (n = 59)	88.2 (n = 97)	χ^2 = 0.700	0.403
Respiratory comorbidities (%)	73.4 (n = 47)	54.5 (n = 60)	χ^2 = 6.098	0.014
Cardiovascular comorbidities (%)	57.8 (n = 37)	63.6 (n = 70)	χ^2 = 0.580	0.446
CRP mg/L [d]	27.3 ± 55.8	51.9 ± 68.7	Z = –2.815	0.005
CRP >10 mg/L (%)	39.1 (n = 25)	60 (n = 66)	χ^2 = 6.295	0.012
Leukocytes (×10^9/L)	10.5 ± 3.8	10.6 ± 4.3	Z = –0.012	0.990
Erythrocytes (×10^{12}/L)	4.8 ± 0.7	4.5 ± 0.6	T = –2.666	0.008
Hematocrit	0.48 ± 0.07	0.46 ± 0.07	T = 0.481	0.149
Hematocrit <41% (%)	17.2 (n = 11)	20 (n = 22)	χ^2 = 0.208	0.648
Blood glucose (mmol/L)	7.6 ± 2.6	7.8 ± 4..8	Z = –0.368	0.713
Prescribed preventive therapy (%) [e]	79.7 (n = 51)	65.5 (n = 72)	χ^2 = 3.956	0.047

[a] BMI - body mass index.
[b] LOH - length of hospital stay.
[c] Parameters of lung function: FEV1 - forced expiratory volume at first second; FVC - forced vital capacity.
[d] CRP - C-reactive protein.
[e] Prescribed preventive therapy - long acting bronchodilators- LABAs, LAMA, theophylline, and inhaled steroids.

age (21). On the contrary, other authors observed high readmission rates for patients younger than 65 years (22), or did not suggest that age could be a predictor variable (15). Our results showed that in the population of patients less than 65 years of age (n = 69) in both studied groups, 48 patients (69.9%) had respiratory comorbidities present. Further, out of this number, 27 patients (84.4%) were in the case group compared to 21 (56.8%) in the control group of patients, showing a significant difference (P = 0.013) (data not shown). This finding indicates that patients under 65 years with respiratory comorbidities have more chance of experiencing a minimum of two hospitalizations in a year. In our circumstances, patients also do not often adhere to prescribed therapy due to poor socioeconomic status and scant health education. Limited knowledge often increases fear for health. It is possible that older patients from our study used preventive therapy prescribed during the index hospitalization (long-acting bronchodilators-LABAs, LAMA, theophylline, and inhaled steroids), more often due to more pronounced fear for their own health. Nevertheless, our multivariate analysis did not show a predictive value of prescribed preventive therapy, although its efficacy for prevention of acute exacerbations has been well established (17,23,24). Treatment with inhaled LABAs and ICS decreased exacerbation frequency in a population of COPD patients older than 70 years (21). In our study, preventive therapy was prescribed more often to the frequent exacerbators group, which is a younger group of patients and less adherent to prescribed medication. This finding could contribute to confounding since we had limited information about compliance. Similar observations have been presented previously (2). Further examinations are needed to confirm this claim.

Higher exacerbation frequency is more likely to be reported in patients with longer length of hospital stay (LOH) according to our results. Prolonged time spent in

Table 2. Univariate analysis of possible predictors of frequent severe COPD exacerbations.

Variables	Odds ratio (95% CI)	P -value
Age, years	0.948 (0.917–0.980)	0.002
Sex	1.047 (0.542–2.021)	0.892
BMI, kg/m^2 [a]	1.054 (1.000–1.111)	0.05
Current smoker (%)	0.842 (0.455–1.561)	0.585
Smoking (pack-years)	1.005 (0.993–1.017)	0.426
LOH stay [b]	1.121 (1.048–1.199)	0.001
FEV1, predicted (%) [c]	0.962 (0.940–0.985)	0.001
FEV1 <50 % (%) [c]	2.753 (1.292–5.868)	0.009
FVC	0.983 (0.968–0.998)	0.027
FEV1/FVC ratio, (%) [c]	0.952 (0.923–0.982)	0.002
Comorbidities (%)	1.581 (0.537–4.661)	0.406
Respiratory comorbidities (%)	2.304 (1.179–4.501)	0.015
Cardiovascular comorbidities (%)	0.783 (0.417–1.470)	0.447
CRP mg/L [d]	0.994 (0.989–1.000)	0.044
CRP >10 mg/L	0.427 (0.227–0.803)	0.008
Leukocytes ($\times10^9$/L)	0.988 (0.919–1.063)	0.749
Erythrocytes ($\times10^{12}$/L)	1.938 (1.170–3.208)	0.01
Hematocrit	27.605 (0.303–2512.921)	0.149
Hematocrit <41% (%)	0.830 (0.373–1.848)	0.648
Glycemia (mmol/L)	0.972 (0.890–1.062)	0.533
Prescribed preventive therapy (%) [e]	2.071 (1.003–4.274)	0.049

[a] BMI - body mass index.
[b] LOH - length of hospital stay.
[c] Parameters of lung function: FEV1 - forced expiratory volume at first second; FVC - forced vital capacity.
[d] CRP - C-reactive protein.
[e] Prescribed preventive therapy - long acting bronchodilators- LABAs, LAMA, theophylline, and inhaled steroids.

the hospital due to COPD exacerbation may indicate more fragile patients with comorbidities like respiratory disease, heart failure, or diabetes (25–27), who are more susceptible to exacerbations. Thus, these patients could more often experience at least two exacerbations in a year. Similar findings have been reported earlier (28,29), suggesting that ischemic heart disease might contribute to treatment failure, while elevated blood sugar level might support the growth of pathogens in the airway, promote inflammation, and increase the frequency of exacerbations (29). At the same time, in our study, cardiovascular comorbidities and glucose level were not associated with frequent exacerbations. Other authors have outlined the same conclusion as we noticed regarding LOH, despite the fact that their basic results were the opposite: shorter LOH was associated with repeated hospitalization (25). As suggested before, prolonged LOH is associated with disease severity (25,29), which is aligned with our findings showing that patients with more exacerbations had more severe forms of COPD, additionally aggravated by respiratory comorbidities (as shown in Table 1). Furthermore, these comorbidities may impair lung function additionally, disturb the overall health status, and limit the patient's ability to cope with acute illness and therefore increase the susceptibility to repeated hospitalization (25,29). Respiratory comorbidities were more often reported among the cases in our study. Their association with frequent exacerbations was also confirmed after adjustment (as shown in Table 3).

Impairment of lung function as well as treatment response has been well established as a risk factor for frequent exacerbations (6,8,13,30), which is not in

Table 3. Stepwise multivariate analysis of possible predictors of frequent severe COPD exacerbations.

Variables	Odds ratio (95% CI)	P-value
Age, years	0.954 (0.918–0.991)	0.015
LOH stay [a]	1.128 (1.047–1.214)	0.001
FEV1/FVC ratio (%) [b]	0.955 (0.923–0.988)	0.007
CRP >10 mg/L	0.387 (0.185–0.808)	0.011
Respiratory comorbidities (%)	2.241 (1.023–4.907)	0.044

[a] LOH - length of hospital stay.
[b] Parameters of lung function: FEV1 - forced expiratory volume at first second; FVC - forced vital capacity.

accordance with our results. If measuring spirometry during a clinically stable period, at least 2 months after hospitalization, lower FEV1 values would be associated with a higher risk of readmission (31). Moreover, patients who experienced a 2-month treatment (ICS/LABA/LAMA) response and FEV1 improvement had greater reductions in exacerbation risk in the following year (30). We found no association between FEV1 predicted, FEV1 <50% (GOLD staging III and IV), and exacerbation frequency in multivariate regression, although both variables showed significance in univariate analysis. Our study is not the only one that reported a lack of relationship between decreased lung function and exacerbation frequency (2,25,31). Explanations proposed earlier suggest that this finding may be due to relatively small variations in FEV1 in the studied population of 43 ± 16 (25) and the spirometry testing being performed during hospitalization, not in a stable form of the disease (31). Similar variations in FEV1 values measured during hospitalization were noticed in our study: 36.5 ± 14.3 and 45.4 ± 15.5 (as shown in Table 1). Our results indicated that the FEV1/FVC ratio might be a better predictor of future events during the course of COPD. Similar, the exacerbation onset in the next 6 months is associated with lower FEV1/FVC ratios (32). Recent observations showed univariate association of similar parameters, FEV1 % predicted and FEV1/FVC, with frequent exacerbations that were lost in multivariate analysis for both variables (16), while others found no difference in FEV1 % predicted and FEV1/IVC between groups (33). Many guidelines suggest the FEV1/FVC ratio for assessment of the airway obstruction. However, interpretation of this test could be challenging since it depends not only on the degree of airflow limitation estimated based on the value of FEV1, which was significant lower in the case group of patients in our study, but it also depends on the value of FVC. Since FVC represent a volume of exhaled air, its value is strongly influenced by duration of expiratory time. It was established that the longer the expiratory time is, the higher the value of FVC, and vice versa (34). Patients with airflow obstruction find it difficult to empty their lungs and hence need more time for exhalation, as do older patients. In our study, the case group of patients had significantly lower levels of FEV1, FVC, and FEV1/FVC ratio. This result suggests that expiratory flow was slower in the control group of patients since they had significantly higher FVC values (as shown in Table 1). During air exhalation, expiratory muscles are activated and therefore patients could get tired during spirometry testing, which is more frequent in patients with obstruction but also in older patients. This could explain the significant difference in FVC values in favor of the control group, which was a significantly older group (as shown in Table 1). However, valid expiration during spirometry testing is considered to be one lasting at least 6 s (35), suggesting that our hypothesis could be confirmed or invalidated by assessing values of FEV6 measurements, which is a more stable indicator of expiration accuracy (36) independently related to annual lung function decline (37) and eliminates the potential age factor in interpretation of FVC values. Further studies are needed to investigate this issue. It would also be useful to determine the cut-off values of the FEV1/FVC ratio, which could be helpful in anticipating the course of COPD. Our results suggested that younger patients suffering from COPD with lower FEV1, FVC, and FEV1/FVC ratio have more chance of having at least two hospitalizations in a year.

Interestingly, we found a significant difference in CRP levels in favor of the control group. Correlation between serum CRP levels and clinical parameters is still under discussion and the conclusions are not definitive. It was noticed that CRP level correlates with degree of pulmonary inflammation during the stable phase of COPD and could have a predictive value in the COPD course (38), with increased incidences of hospitalization due to COPD in individuals with higher levels of CRP (39,40).

Concentration of CRP level is also found to be related to the presence of airflow obstruction in COPD patients (41) and lung function parameters FEV1 and FVC (42), while authors of other studies failed to demonstrate this association (43,44). However, all of these studies observed patients in the stable form of the disease and most of them considered CRP level as a categorical variable (CRP <3 mg/L versus CRP >3 mg/L). In the present study we considered CRP level as a continuous variable and observed a pool of patients in exacerbation, not in the stable form of the disease. Since we could not confirm a predictor value for CRP level as a continuous variable (CRP mg/L) in univariate regression analysis (as shown in Table 2), we performed additionally analyses with CRP level as a categorical variable (CRP <3 mg/L versus CRP >3 mg/L) with no statistical difference (data not shown) and also as CRP <10 mg/L versus CRP >10 mg/L, since in healthy young adult volunteer blood donors, the 99th percentile of CRP is established at a level of 10 mg/L (45). Interestingly, second analyses showed a higher frequency of CRP of >10 mg/L in the infrequent exacerbators group of patients, contrary to previous results (38). Concentration of CRP is expected to be higher in frequent exacerbator groups of patients due to the enhanced inflammatory response (40). It was reported that CRP is the most variable biomarker among several potential biomarkers in COPD (46). Accordingly, it is possible that these variations of CRP concentration between the stable phase of COPD and exacerbation are more pronounced in the control group of patients. This group of patients could have less enhanced inflammatory response and thus less elevated CRP concentration during the stable phase of COPD, but during exacerbations, the control group of patients could have a greater increase of CRP concentration and more elevated values of this parameter than the case group of patients. Since they were an older group of patients with possible impairment of the immune system, and since CRP levels can predict bacterial exacerbation in patients with COPD (39), it is possible that bacterial infection was more often present in the control group of patients, causing a greater increase of CRP. This more intensive inflammatory response during exacerbation could somehow help with eradication of microorganisms and postpone the next exacerbation.

We are aware of several limitations of our study. First, since bronchodilator testing was conducted for only a small number of patients, we used prebronchodilator values instead, which is in contrast to guideline recommendations (1). It remains unclear how this would affect the outcomes. Second, the case-control approach predisposes the present study to recall bias. Finally, the number of patients' medical files that we included in the study could be perceived as modest and may not represent the COPD population at large.

Despite these limitations, our study suggests that age, length of hospital stay, FEV1/FVC ratio, CRP level, and the presence of respiratory comorbidities could be used to anticipate future exacerbations requiring hospitalization of COPD patients. Adherence to prescribed therapy also influences the course of COPD. Concentration of CRP has predictive value for COPD exacerbation rates and should be measured during both the stable form of COPD and also during exacerbation. Learning to recognize, adjust, diminish, or eliminate these and a number of other risk factors may improve patient quality of life and help them to spend less time in hospital environments. Further prospective studies are necessary to resolve the significance of all potential predictors of the COPD exacerbation rate.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis. Management and Prevention of Chronic Obstructive Pulmonary Disease. Barcelona, Spain: GOLD; 2014.
2. Wan E, DeMeo D, Hersh C, Shapiro S, Rosiello R, Sama S, Fuhlbrigge A, Foreman M, Silverman E. Clinical predictors of frequent exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD). Respir Med 2011; 105: 588-594.
3. Hurst J, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas D, Agusti A, Macnee W et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010; 363: 1128-1138.
4. Parikh R, Shah TG, Tandon R. COPD exacerbation care bundle improves standard of care, length of stay, and readmission rates. Int J Chron Obstruct Pulmon Dis 2016; 11: 577-583.
5. Montserrat-Capdevila J, Godoy P, Marsal JR, Barbé F, Galván L. Risk of exacerbation in chronic obstructive pulmonary disease: a primary care retrospective cohort study. BMC Fam Pract 2015; 16: 173.
6. Burgel PR, Nesme-Meyer P, Chanez P, Caillaud D, Carre P, Perez T, Roche N. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest 2009; 135: 975-982.
7. Niewoehner DE, Lokhnygina Y, Rice K, Kuschner WG, Sharafkhaneh A, Sarosi GA, Krumpe P, Pieper K, Kesten S. Risk indexes for exacerbations and hospitalizations due to COPD. Chest 2007; 131: 20-28.
8. Hoogendoorn M, Feenstra TL, Hoogenveen RT, Al M, Molken MR. Association between lung function and exacerbation frequency in patients with COPD. Int J Chron Obstruct Pulmon Dis 2010; 5: 435-444.

9. Hurst JR. Exacerbation phenotyping in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011; 184: 625-626.

10. Merinopoulou E, Raluy-Callado M, Ramagopalan S, MacLachlan S, Khalid JM. COPD exacerbations by disease severity in England. Int J Chron Obstruct Pulmon Dis 2016; 11: 697-709.

11. Faganello MM, Tanni SE, Sanchez FF, Pelegrino NR, Lucheta PA, Godoy I. BODE index and GOLD staging as predictors of 1-year exacerbation risk in chronic obstructive pulmonary disease. Am J Med Sci 2010; 339: 10-14.

12. Ozyilmaz E, Kokturk N, Teksut G, Tatlicioglu T. Unsuspected risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease. Int J Clin Pract 2013; 67: 691-697.

13. Marin JM, Carrizo S, Casanova C, Martinez-Camblor P, Soriano J, Agusti AG, Celli BR. Prediction of risk of COPD exacerbations by the BODE index. Respir Med 2009; 103: 373-378.

14. Beeh KM, Glaab T, Stowasser S, Schmidt H, Fabbri LM, Rabe KF, Vogelmeier CF. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respir Res 2013; 14: 116.

15. Kasirye Y, Simpson M, Mamillapalli CK, Epperla N, Liang H, Yale SH. Association between blood glucose level and outcomes in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease. WMJ 2013; 112: 244-249.

16. Brusse-Keizer M, van der Palen J, van der Valk P, Hendrix R, Kerstjens H. Clinical predictors of exacerbation frequency in chronic obstructive pulmonary disease. Clin Respir J 2011; 5: 227-234.

17. Abudagga A, Sun SX, Tan H, Solem CT. Exacerbations among chronic bronchitis patients treated with maintenance medications from a US managed care population: an administrative claims data analysis. Int J Chron Obstruct Pulmon Dis 2013; 8: 175-185.

18. Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB; Respiratory Effectiveness Group. Predicting frequent COPD exacerbations using primary care data. Int J Chron Obstruct Pulmon Dis 2015; 10: 2439-2450.

19. Jurado Gamez B, Feu Collado N, Carlos Jurado Garcia J, Garcia Gil F, Munoz Gomariz E, Jimenez Murillo L, Munoz Cabrera L. Home intervention and predictor variables for rehospitalization in chronic obstructive pulmonary disease exacerbations. Arch Bronconeumol 2012; 49: 10-14.

20. McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest 2007; 132: 1748-1755.

21. Liu D, Peng SH, Zhang J, Bai SH, Liu HX, Qu JM. Prediction of short term re-exacerbation in patients with acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015; 10: 1265-1273.

22. Baker CL, Zou KH, Su J. Risk assessment of readmissions following an initial COPD-related hospitalization. Int J Chron Obstruct Pulmon Dis 2013; 8: 551-559.

23. Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012; 7 CD002991.

24. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013; 8 CD006826.

25. Bahadori K, FitzGerald JM, Levy RD, Fera T, Swiston J. Risk factors and outcomes associated with chronic obstructive pulmonary disease exacerbations requiring hospitalization. Can Respir J 2009; 16: 43-49.

26. Wang Y, Stavem K, Dahl FA, Humerfelt S, Haugen T. Factors associated with a prolonged length of stay after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Int J Chron Obstruct Pulmon Dis 2014; 9: 99-105.

27. Roche N, Rabbat A, Zureik M, Huchon G. Chronic obstructive pulmonary disease exacerbations in emergency departments: predictors of outcome. Curr Opin Pulm Med 2010; 16: 112-117.

28. 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.

29. Gaude GS, Rajesh BP, Chaudhury A, Hattiholi J. Outcomes associated with acute exacerbations of chronic obstructive pulmonary disorder requiring hospitalization. Lung India 2015; 32: 465-472.

30. Calverley PM, Postma DS, Anzueto AR, Make BJ, Eriksson G, Peterson S, Jenkins CR. Early response to inhaled bronchodilators and corticosteroids as a predictor of 12-month treatment responder status and COPD exacerbations. Int J Chron Obstruct Pulmon Dis 2016; 11: 381-390.

31. Tsoumakidou M, Tzanakis N, Voulgaraki O, Mitrouska I, Chrysofakis G, Samiou M, Siafakas NM. Is there any correlation between the ATS, BTS, ERS and GOLD COPD's severity scales and the frequency of hospital admissions? Respir Med 2004; 98: 178-183.

32. Make BJ, Eriksson G, Calverley PM, Jenkins CR, Postma DS, Peterson S, Östlund O, Anzueto A. A score to predict short-term risk of COPD exacerbations (SCOPEX). Int J Chron Obstruct Pulmon Dis 2015; 10: 201-209.

33. Almagro P, Barreiro B, Ochoa de Echaguen A, Quintana S, Rodríguez Carballeira M, Heredia JL, Garau J. Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease. Respiration 2006; 73: 311-317.

34. Perez-Padilla R, Wehrmeister FC, Celli BR, Lopez-Varela MV, Montes de Oca M, Muiño A, Talamo C, Jardim JR, Valdivia G, Lisboa C et al. Reliability of FEV1/FEV6 to diagnose airflow obstruction compared with FEV1/FVC: the PLATINO longitudinal study. PLoS One 2013; 8: e67960.

35. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P et al. Standardisation of spirometry. Eur Respir J 2005: 26: 319–338.

36. Jing JY, Huang TC, Cui W, Xu F, Shen HH. Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. Chest 2009; 135: 991-998.

37. Prats E, Tejero E, Pardo P, Gavilán A, Galera R, Donado JR, Racionero MÁ, Casitas R, Zapatero A, García-Río F. Prognostic value of the six-second spirometry in patients with chronic obstructive pulmonary disease: a cohort study. PLoS One 2015; 10: e0140855.

38. Dahl M, Nordestgaard BG. Markers of early disease and prognosis in COPD. Int J Chron Obstruct Pulmon Dis 2009; 4: 157-167.

39. Jing Z, Chun C, Ning S, Hong Z, Bei H, Wan-Zhen Y. Systemic inflammatory marker CRP was better predictor of readmission for AECOPD than sputum inflammatory markers. Arch Bronconeumol 2016; 52: 138-144.

40. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; 175: 250-255.

41. Pinto-Plata VM, Müllerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers, and nonsmokers. Thorax 2006; 61: 23-28.

42. de Torres JP, Cordoba-Lanus E, López-Aguilar C, Muros de Fuentes M, Montejo de Garcini A, Aguirre-Jaime A, Celli BR, Casanova C. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. Eur Respir J 2006; 27: 902-907.

43. de Torres JP, Pinto-Plata V, Casanova C, Mullerova H, Córdoba-Lanús E, Muros de Fuentes M, Aguirre-Jaime A, Celli BR. C-reactive protein levels and survival in patients with moderate to very severe COPD. Chest 2008; 133: 1336-1343.

44. Liu SF, Wang CC, Chin CH, Chen YC, Lin MC. High value of combined serum C-reactive protein and BODE score for mortality prediction in patients with stable COPD. Arch Bronconeumol 2011; 47: 427-432.

45. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111: 1805-1812.

46. Dickens JA, Miller BE, Edwards LD, Silverman EK, Lomas DA, Tal-Singer R. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res 2011; 12: 146.