Adam Nowiński, Dariusz Kamiński, Damian Korzybski, Anna Stokłosa, Dorota Górecka

II Department of Lung Diseases, Institute of Tuberculosis and Lung Diseases in Warsaw
Head: Prof. D. Górecka, MD PhD

The impact of comorbidities on the length of hospital treatment in patients with chronic obstructive pulmonary disease

Wpływ chorób współistniejących na długość leczenia szpitalnego u chorych z zaostrzeniem przewlekłej obturacyjnej choroby płuc

Abstract

Introduction: The aim of this study was to assess the relationship between the incidence of comorbidities of chronic obstructive pulmonary disease (COPD) and the duration of hospital stay due to acute AE COPD in a longitudinal prospective study.

Material and methods: We evaluated the number of re-hospitalizations, length of stay, and number of comorbidities in 464 consecutive COPD patients admitted to the tertiary respiratory hospital due to AE COPD enrolled in a longitudinal prospective study from 2005 to 2009.

Results: GOLD II stage COPD patients had 4.1 ± 1.2 comorbidities ($p = 0.002$), stage III 3.4 ± 1.3, and stage IV 3.6 ± 1.2 comorbidities. The duration of hospital stay (median) was longer in more severe conditions. Duration of hospitalization correlated with the urea level ($r = 0.19$ $p < 0.001$), pCO_2 ($r = 0.193$, $p = 0.0003$), HCO_3 ($r = 0.25$, $p < 0.0001$), haemoglobin ($r = -0.18$, $p < 0.001$), and haematocrit ($r = -0.13$, $p = 0.008$). Patients with the risk of readmission had a more severe GOLD stage and were hypercapnic (pCO_2 = 47.6 mm Hg vs. 43.9 mm Hg in those without hospitalization).

Conclusions: Haemoglobin level, hypercapnia, and renal function are predictors of prolonged hospitalization. Patients with a more severe airflow limitation and a higher pCO_2 level reveal an increased risk of readmission to hospital. More severe disease stage and clinical diagnosis of cor pulmonale or bronchiectasis were related to longer hospital stay.

Key words: COPD, comorbidities, COPD exacerbation, hospital treatment length

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent chronic diseases, with a constantly increasing morbidity and mortality rate [1]. Smoking is the most common cause of the disease in developed countries, although the disease may also occur in non-smokers. COPD exacerbations lead to accelerated progression of the disease and constitute an important factor of increased mortality [1].

Chronic obstructive pulmonary disease is primarily a lung disease. Airflow limitation is necessary for its diagnosis [1]. Inflammatory process, characterizing COPD, leads to a radical remodelling of lung parenchyma, small bronchi, and pulmonary vessels, causing emphysema, inflammation of the small bronchi, and pulmonary hypertension. It is also connected with serious extrapulmonary consequences (loss of muscle mass, myopathy) and comorbidities (coronary heart disease, lung cancer, osteoporosis, depression) [2, 3].

Address for correspondence: Adam Nowiński, MD, II Klinika Chorób Płuc, II Department of Lung Diseases, Institute of Tuberculosis and Lung Diseases in Warsaw, Płocka 26 St., 01–138 Warszawa, tel.: +48 (22) 431 21 44, faks: +48 (22) 431 24 54, e-mail: a.nowinski@igichp.edu.pl

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Comorbidities associated with COPD have been identified through epidemiological observational studies. In some cases, causal relations of COPD and comorbidities have also been established. These associations consist mainly of the consideration of COPD as an inflammatory disease, with a "leakage" of inflammatory mediators from lungs into the circulation [3]. The current definition of COPD according to international consensus of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1] and the recommendations of Polish Society of Lung Diseases [4] underlines the systemic nature of the disease. Such a definition of COPD inclines clinicians towards a comprehensive treatment and reveals the complexity of the disease.

In COPD, as in other chronic diseases, the occurrence of comorbidities and systemic effects increases the cost of treatment, with the majority of expenses generated by comorbid diseases [5].

The aim of the study was to analyse the occurrence of comorbidities in patients with COPD exacerbation in relation with the length of hospital stay at the referral centre for pulmonary diseases.

Materials and methods

We analysed data of patients admitted consecutively to the II Department of Respiratory Medicine of the Institute of Tuberculosis and Lung Diseases in Warsaw (IGiChP). These patients were recruited to a long-term prospective study in the years 2005–2009, evaluating the survival in patients with COPD hospitalized due to COPD exacerbation.

Subjects were referred to the department from the Emergency Department as urgent admissions, from specialist outpatient clinics (including 'home oxygen therapy' outpatient clinic for patients with chronic respiratory failure), or transferred from other hospitals in case of difficulty in treatment.

Patients with COPD exacerbation treated with non-invasive or invasive assisted ventilation in a department or intensive care unit were also enrolled in the study provided that they stayed in the II Department of Respiratory Medicine of IGiChP in the period preceding or following treatment within the intensive care unit. The study included patients with principal diagnosis of COPD exacerbation or respiratory failure in the course of COPD exacerbation. In case of relapse of COPD exacerbation, the patients were admitted to the II Department of Respiratory Medicine. The patients' data were collected prospectively. The data for analysis were obtained from the hospital central database. Physicians responsible for treatment of patients enrolled in the study were free to perform any additional tests and examinations. As the patients' overall clinical state improved and if their condition allowed, a 6-minute walk test was performed.

The evaluation included presence of comorbidities, parameters of pulmonary function test and laboratory tests, the percentage of rehospitalisation in the II Department of Respiratory Medicine of IGiChP, as well as the length of hospital stay. Information about coexisting diseases was obtained from the final diagnoses at hospital discharge. Potential predictors of prolonged hospitalization were analysed. The Charlson Comorbidity Index (CCI) was calculated for all patients. The Charlson Comorbidity Index is a tool aggregating data related to comorbidities, which can also be used for prognostic purposes, including treatment cost estimation [6]. Each coexistent condition (comorbidity) was assigned weight (1–6, see Appendix 1) — giving a total CCI score on aggregation. An index score exceeding 2 was associated with an increased risk of death from concomitant diseases. The following variables were studied as factors influencing the length of hospital stay: gender, age, percentage of predicted forced expiratory volume in 1 second (FEV_1), arterial partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), C-reactive protein (CRP), parameters of available laboratory tests, CCI, and each particular comorbidity.

Statistical Analysis

Descriptive data were presented using means ± standard deviations or medians. Chi-square test was used for categorical data and One-Way ANOVA or ANOVA on Ranks were applied to categorize continuous variables into groups. Correlations between each of the laboratory parameters and the length of hospital stay were investigated by assessing the Pearson correlation coefficient. Multiple regression analysis was performed to assess the relationships between the parameters. Differences in the length of hospitalization between patients with and without particular comorbidity were analysed using Student's t-test or Wilcoxon-Mann rank sum test, depending on the fulfilled criteria for normal distribution.

Results

The study included 464 patients. Table 1 displays basic clinical and demographic data. Results are expressed using means ± standard deviations. Data not meeting the criteria of normal distribution are presented as median and quartile values.

Table 1. Characteristics of studied group

	Studied group	GOLD II	GOLD III	GOLD IV
Number of patients (n)	465	35	139	287
Age (years)	71.5 ± 8.7	71.8 ± 9.2	71.6 ± 8.6	71.3 ± 8.4
Number of women (n) and percentage in groups (%)	191 (41%)	12 (35%)	62 (44%)	114 (39%)
Men (n)	274 (59%)	23 (65%)	77 (56%)	173 (61%)
FEV_1 [l]	0.94 ± 0.51	1.58 ± 0.61	1.01 ± 0.30	0.57 ± 0.17
FEV_1% of predicted	35.8 ± 16.6	61.5 ± 9.4	38.7 ± 6.08	21.6 ± 4.9
FVC [l]	2.19 ± 0.79	2.78 ± 0.98	2.37 ± 0.54	1.72 ± 0.62
FVC% of predicted	64.2 ± 19.6	83.8 ± 15.8	71.1 ± 15.2	49.4 ± 12.8
PaO_2 [mmHg]	62.1 ± 26.8	63.9* (59.5; 70.4)	62.8* (57.4; 69.9)	58.3* (52.4; 67.5)
$PaCO_2$ [mmHg]	46.8 ± 10.7	37.9* (33.4; 40.4)	40.8* (36.8; 47.0)	48.7* (42.4; 56.5)
HCO_3 [mmHg]	29.633 ± 5.234	25.3* (24.2; 26.3)	26.6* (24.0; 29.5)	30.6* (28.2; 34.5)
Haemoglobin [g/dl]	14.0 ± 1.8	13.5 ± 1.39	13.9 ± 1.7	14.1 ± 1.7
Hematocrit (%)	43.5 ± 5.6	41.4* (37.9; 44.2)	42.5* (38.9; 45.6)	43.8* (40.4; 47.6)
Total cholesterol [mg/dl]	191.4 ± 42.6	179.4 ± 58.0	192.4 ± 40.1	192.8 ± 42.1
LDL [mg/dl]	105.9 ± 34.4	96.5 ± 46.2	103.5 ± 32.7	108.71 ± 33.3
HDL [mg/dl]	62.7 ± 24.5	53.5 ± 21.2	57.0 ± 18.8	58.0 ± 22.5
Creatinine [mg/dl]	0.9 ± 0.3	0.90* (0.78; 1.05)	0.89 (0.75; 1.11)	0.80* (0.70; 1.00)
Urea [mg/dl]	40.9 ± 21.5	36.0 (25.7; 53.0)	37.0 (28.0; 47.0)	36.0 (27.0; 50.0)
C-reactive protein [mg/dl]	4.9 (1.6; 12.3)	5.2 (1.8; 11.3)	5.7 (2.6; 22.3)	4.4 (1.8; 19.3)
6-minute walking distance [m]	265.6 ± 132.5	290.0* (184.0; 432.5)	241.0 (164.0; 365.7)	241.0 (164.0; 336.0)

*Statistically significant difference $p < 0,05$; GOLD — Global Initiative for Chronic Obstructive Lung Disease; FEV_1 — forced expiratory volume in 1 second; FVC — forced vital capacity; PaO_2 — arterial partial pressure of oxygen; $PaCO_2$ — partial pressure of carbon dioxide in the arterial blood; HCO_3 — hydrogen carbonate; LDL — low density lipoproteins; HDL — high density lipoproteins

There were no mild COPD patients in the study group and relatively few patients with a moderate stage of COPD (GOLD stage II), who required hospital treatment (n = 35). The largest group hospitalized due to COPD exacerbation were patients with a severe form of the disease (62% of all patients). Male patients prevailed among COPD patients who required hospitalization due to disease aggravation. The subjects were elderly patients (mean age 71.5 ± 8.7 years, Table 1) with a tendency towards hypoxemia (PaO_2 62.1 ± 26.8 mm Hg) that varied between patients in different stages of the disease with statistical significance. Gasometric parameters of increased partial pressure of carbon dioxide and hydrogen carbonate, with levels of hypercapnia and bicarbonate concentrations elevated with increasing severity of the disease, were observed. At the same time, patients had an increased level of haematocrit and decrease in serum creatinine.

Patients with a moderate disease, after improvement of their overall state, performed better in the 6-minute walk test, compared to patients with an advanced disease.

The number of comorbidities, age, and median values of hospital stay are presented in Table 2. Patients treated in hospital due to COPD exacerbation presented with a substantial number of comorbidities; however, patients with moderate disease had a significantly higher number of comorbidities compared to patients with severe or very severe disease. The percentage of patients requiring re-admission to hospital because of COPD was higher with increasing severity of the disease. In the group with moderate disease, only 8.6% of patients were re-admitted within a year due to COPD exacerbation, whereas in the group with a very severe form, 25% of patients required at least one re-hospitalization within a year. Patients in more advanced stages of the disease required prolonged hospital treatment.

The main comorbidities in the study group are described in Table 3. The most common comorbidities were cardiovascular diseases such as hypertension (38% of all patients), cor pulmonale, and left ventricular failure (in total 35%). Diabetes appeared to be a very common coexistent disease

Table 2. Comorbidities and hospital treatment

Gold stage	*Number of comorbidities*	*Percentage of readmissions*	*Length of hospital treatment (days); median, quartile*	*Charlson Index (score)*
I (n = 0)	–	–	–	–
II (n = 35)	4.1 ± 1.2*	8.6	13.0* (7.0; 18.0)	2.0 (1.25; 2.0)
III (n = 139)	3.4 ± 1.3	20.0	14.0* (8.0; 18.0)	2.0 (1.0; 3.0)
IV (n = 287)	3.6 ± 1.2	28.2	15.0* (11.0; 22.0)	2.0 (1.0; 3.0)
Total (n = 464)	3.6 ± 1.2	24.8	15.0 (9.0; 20.0)	2.1 ± 1.1

*Statistically significant difference p < 0,05; GOLD — Global Initiative for Chronic Obstructive Lung Disease

Table 3. Most common comorbidities

Diagnosis	Number of patients	Percentage of total number of patients
Hypertension	176	37.8
Cor pulmonale	127	27.3
Diabetes	79	16.9
Thyroid diseases	65	13.9
Coronary disease	51	10.9
Obesity	49	10.5
Peptic ulcer	44	9.4
Bronchiectases	35	7.5
Heart failure	35	7.5
Anaemia	23	4.9
Renal failure	23	4.9
Sleep apnea	17	3.6
Hyperlipidaemia	14	3.0
Lung cancer	8	1.7
Osteoporosis	4	0.9

(17%) as well as thyroid diseases (14%). Obesity was present in 10% of all patients. The length of hospital stay was compared between patients with different comorbidities. COPD patients who were diagnosed with cor pulmonale or bronchiectasis required longer hospital treatment. Patients with peptic ulcer disease and hyperlipidaemia stayed in hospital for a shorter time.

Pearson correlation analysis revealed that the length of hospital stay correlated with the concentration of blood urea ($r = 0.19$, $p < 0.001$), pCO_2 ($r = 0.193$, $p = 0.0003$), HCO_3 ($r = 0.25$, $p < 0,0001$), haemoglobin level ($r = -0.18$, $p < 0.001$), and haematocrit level ($r = -0.13$, $p = 0.008$) (Table 4).

Patients with increased risk of re-admission due to COPD manifested hypercapnia (pCO_2 = 47.6 mm Hg vs. 43.9 mm Hg in patients without re-admissions).

Additionally, the association of individual comorbid conditions with the duration of hospital stay was assessed. Multiple regression analysis was used to evaluate the available continuous variables as predictors of length of hospital stay. Statistically significant were: urea and creatinine serum level and pCO_2 of arterialized venous blood ($p < 0.05$).

Patients who had reduced haemoglobin concentration values on admission required a longer hospital stay compared to patients with normal or elevated levels of haemoglobin (Table 5).

In regression analysis the usefulness of CCI score as a predictive factor of the length of hospital treatment was evaluated. There was no correlation between the CCI score and the length of hospital stay ($R = 0.06$, $p = 0.192$).

Table 4. Selected laboratory findings and hospital length correlations

	Laboratory findings	
Hospital stay length	**p value**	**Correlation coefficient**
Creatinine	0.488	–0.0344
Urea	0.000128	0.191
pCO_2	0. 000106	0.192
pO_2	0.187	–0.0650
pH	0.784	0.0143
proBNP	0.743	–0.0393
Cholesterol	0.896	0.00913
CRP	0.761	–0.0197
Red blood cells	0.00411	–0.135
Hematocrit	0.00849	–0.124
Haemoglobin	0.0000976	–0.183

proBNP — brain natriuretic peptide; CRP — C-reactive protein

Table 5. Haemoglobin level in the blood and the length of hospital stay

	Length of hospitalization (days)
Haemoglobin level < 13.5 g/dL men < 12.0 g/dl women (days, median, quartile) Number of patients, n = 101	15.0 (8.7; 22,2)*
Haemoglobin level 13.0–17.5 g/dL men12.0–17.5 g/dl women (days, median, quartile) Number of patients, n = 338	14.0 (10.0; 20,0)*
Elevated haemoglobin level > 17.5 g/dL (days, median, quartile) Number of patients, n = 6	8.0 (4.0; 14,0)*

*p < 0,05

Discussion

The present results indicate that patients with COPD exacerbations who require hospitalization in the II Department of Lung Diseases suffer from multiple comorbidities. The study group was dominated by patients with severe and very severe disease, whereas patients with moderate COPD (GOLD stage II) required admission to hospital due to COPD exacerbation, when a larger number of comorbidities existed. This leads to the assumption that comorbidities were a very important factor influencing the necessity of hospital treatment in COPD exacerbations in this group of patients. This observation is consistent with the GOLD recommendations as well as the guidelines of the Polish Society of Lung Diseases according to which, major co-morbidities were one of the reasons of necessary hospital treatment in case of COPD exacerbation [1, 4].

Similarly to the present study, a significant number of comorbidities in COPD patients randomly selected from the health program was observed by Mapel and colleagues [7]. In the group of 200 patients with COPD they reported an average of 3.7 chronic diseases, while in the control group (without a diagnosis of COPD) the mean number of chronic diseases was 1.8.

The most common comorbidities in the study group were cardiovascular diseases. A particularly large number of patients admitted to hospital because of exacerbation had hypertension, heart failure, and coronary heart disease. This is consistent with the results of other studies, e.g. a study by Sin et al. [8], which show that systemic inflammation in COPD is causally associated with an increased risk of cardiovascular diseases. Moreover, COPD exacerbations, leading to an increase of the inflammatory process intensity (as measured by CRP levels), translate into an increased risk of death from heart attack and stroke in patients with a history of COPD exacerbation [9]. Unfortunately, the present study does not provide enough data to assess the correlation of CRP levels and coexistent diseases, as CRP values were obtained during exacerbation, with unknown levels during a long-term

Table 6. Length of hospital stay and comorobidities

Diagnosis	Patients with diagnosis of comorbidities Length of hospitalization (days, median, quartile)	Patients without diagnosis of comorbidities Length of hospitalization (days, median, quartile)	Statistical significance
Hypertension	14.0 (9.0; 20.0)	14.0 (9.0; 20.0)	p = 0.62
Cor pulmonale	16.0 (11.0; 22.0)	14.0 (9.0; 20.0)	p = 0.015
Diabetes	14.5 (9.0; 20.5)	15.0 (12.0; 20.0)	p = 0.6
Thyroid diseases	15.0 (11.7; 18.2)	14.5 (9.0; 21.0)	p = 0.57
Coronary disease	14.0 (9.0; 18.0)	15.0 (9.0; 21.0)	p = 0.36
Obesity	14.0 (9.0; 18.0)	15.0 (9.0; 21.0)	p = 0.24
Peptic ulcer	11.5 (6.2; 20.0)	15.0 (10.0; 21.0)	p = 0.028
Bronchiectases	17.0 (13.5; 23.0)	14.0 (9.0; 20.0)	p = 0.012
Heart failure	16.0 (12.0; 21.0)	14.0 (9.0; 20.0)	p = 0.099
Anaemia	14.0 (9.0; 23.0)	15.0 (9.0; 20.0)	p = 0.896
Renal failure	18.0 (11.0; 29.0)	14.0 (9.0; 20.0)	p = 0.109
Sleep apnea	14.0 (10.0; 19.5)	15.0 (9.0; 20.2)	p = 0.80
Hyperlipidaemia	11.0 (3.7; 16.2)	15.0 (9.0; 21.0)	p = 0.042
Lung cancer	15.5 (4.2; 19.7)	15.0 (9.0; 21.0)	p = 0.575
Osteoporosis	17.5 (9.5; 36.0)	15.0 (9.0; 20.0)	p = 0.517

follow-up of stable period of the disease. The average values of CRP increase appeared to be the factor identified as correlating with cardiovascular diseases in literature. The difference in gasometric parameters between the stages of the disease was found to be statistically significant by the authors of this work. Patients with more severe stages presented with lower oxygen partial pressure and, at the same time, higher partial pressure of carbon dioxide and bicarbonates. Differences in PaO_2 in the investigated groups require caution in their interpretation due to some measurement interference. In some patients, oxygen therapy was started before blood sampling and continued at the time of measurement. Therefore, a wide range of PaO_2 measurement results was noted — depending on inspired air oxygen content. Patients with more severe disease had a higher haematocrit level. This is associated with compensatory overproduction of red blood cells in response to hypoxemia. Approximately 5% of the patients had clinically diagnosed anaemia (mainly in the course of chronic diseases), and decreased haemoglobin concentration correlated with the length of hospital stay. Patients with anaemia stayed in hospital for longer period than patients with normal haemoglobin level or polycythaemia. This suggests that patients developing anaemia in the course of chronic disease (including COPD) have worse prognosis than patients who compensate hypoxemia with polycythaemia. Similar conclusions were drawn by Similowski et al., who retrospectively analysed 2524 patients treated with oxygen at home [10]. Interestingly, in our group, physicians treating patients with reduced haemoglobin levels suggested the diagnosis of anaemia far too rarely. In 101 of 460 patients, haemoglobin concentration on admission was below 13.5 g% in males and 12.0 g% in females, and only 5% of all patients were eventually diagnosed with anaemia.

It was found that patients with stage IV COPD had a lower serum creatinine level comparing to patients with lower stages. This may be associated with the known mechanism of loss of muscle mass in patients with more severe stages of COPD [11], which in turn leads to a reduction in muscle metabolism and hence a lower production of creatine/creatinine. However, renal function was an important factor influencing the treatment of exacerbations — the concentration of urea, which is independent of muscle mass, correlated with the length of hospital stay. Patients with higher concentrations of blood urea required a longer hospital stay. Perhaps the assessment of serum creatinine is not the best method of assessing renal function in patients with COPD, and in these patients the use of other, muscle independent, biochemical markers of renal function is necessary. The

need to verify the relationships of renal function and COPD is also recognized by other authors, as the chronic renal failure is not usually classified as typical COPD comorbidity [12].

The assessment of the risk of hospital re-admission in the present material may be biased due to the applied methodology. We analysed only re-admissions to IGiChP, not re-admissions to any other hospitals. However, due to the fact that, in case of a relapse, patients who were treated in the II Department of Lung Diseases usually return to the same department, this assessment is justified. Patients requiring frequent hospitalizations met the criteria for more advanced stages of the disease according to GOLD classification and usually manifested symptoms of respiratory failure.

The overall evaluation and prognosis of patients with COPD requires not only the assessment of primary disease, but also of comorbidities. Taking into account the fact that treatment of COPD exacerbations is associated with a simultaneous treatment of many different diseases can lead to a better understanding of the nature of the disease.

CCI is a useful tool to estimate the expected survival in patients with heart failure, AIDS, or cancer [6]. In the present study, it was used to predict the length of hospital stay, but this goal was not achieved. In case of COPD, factors based on the assessment of respiratory function parameters (FEV_1) and the consequences of systemic disease are rather used as prognostic variables. The best-studied and most widely used tool is the BODE index (body mass index, airflow obstruction, dyspnoea, exercise capacity) [13].

Conclusions

Chronic obstructive pulmonary disease patients requiring hospital treatment due to exacerbation present with numerous co-morbidities. More severe stage of the disease, clinical diagnosis of cor pulmonale, and bronchiectasis is associated with prolonged hospital stay. Reduced haemoglobin, hypercapnia, and laboratory parameters of renal failure are associated with the risk of prolonged hospitalization. Risk of re-admission is greater in patients with severe airway obstruction and hypercapnia.

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Annex 1. Charlson's Comorbidity Index (according to [6])

Diagnosis	CCI
Myocardial infarction	1
Heart failure	1
Hypertension	1
Brain vascular disease	1
Dementia	1
Chronic bronchitis	1
Connective tissue disease	1
Peptic ulcer	1
Minor liver diseases	1
Diabetes	1
Hemiplaegia	2
Minor renal failure	2
Diabetes + terminal heart failure	2
Any tumor	2
Leucaemia	2
Myeloma	2
Serious liver disease	3
Metastatic solid tumor	6
AIDS	6