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Clinical and Laboratory Characteristics of Patients Affected by COPD Exacerbations

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Abstract

Background: COPD exacerbations are a major cause of morbidity and mortality, which are accompanied with damaging of quality of life, decline of pulmonary function and great consumption of medical care resources. Early and adequate recognition of the acute exacerbation, as well as the individualized treatment is important to minimize mortality, morbidity and the worsening of lung function.

Aims: Clinical-laboratory characteristics of patients affected by COPD exacerbations.

Study Design: This is a prospective observational study conducted in Regional Hospital Fier.

Methods: 56 patients with COPD stages III and IV in a state of exacerbation were enrolled in the study.The study data are collected according to the protocol as well as to the anamnestic clinical and laboratic examinations. At the first consultation, due to COPD exacerbations and after 21 days, CRP, IL 6, PARC/CCL18, cellular content of sputum and blood have been defined. All the collected data were first presented in Microsoft-Excel and then they were exported in SPSS (Statistical Package for Social Sciences) 20.0 and Medstat. The statistical analysis was performed after the above mentioned process. All cathegoric variables (nominal, including the binary, dychotomic scale and ordinal), the absolute values and respective percentages were calculated too. For all numerical variables, where the data was subjected to a normal spread, the mathematical averages ± respective standard deviations were calculated. The data was represented through simple and compound charts, as well as graphs. The values of $p \leq 0.05$ were considered significant.

Results: AECOPD has been predominant in the older age, males, more often those of rural origin, workers, and smokers. Nearly all the patients have concomitant diseases (91.1%), predominantly cardiovascular diseases (56.2%). All AECOPD patients manifested dyspnoea, an increase of sputum quantity (76.8%) and sputum purulent (58.9%). According to exacerbation types most of patients (57.2%) have been of type I.In AECOPD there has been an increase of total cell sputum count and blood leukocytosis, decreasing after 21 days ($P<0.0001$).NRL at exacerbation and after 21 days resulted respectively 7.464±12.922 (from 1.04 to 97.9) and 2.509±1.18 (from 0.71 to 7.09) ($p= 0.004$).The CRP, IL6, PAR/CCL18 levels have resulted higher in AECOPD patients in comparison to those with stable COPD.

Conclusion: Clinical symptoms and biologic markers can evaluate COPD exacerbations and its return to a stable state.

Keywords: COPD, AECOPD, Biomarkers

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INTRODUCTION

COPD exacerbations (AECOPD) are a major cause of morbidity and mortality, which are accompanied with damaging of quality of life, decline of pulmonary function and great consumption of medical care resources. Early and adequate recognition of the acute exacerbation, as well as the individualized treatment is important to minimize mortality, morbidity and the worsening of lung function.

Change in symptoms has been used to define the exacerbation clinically (1), whereas the change in therapy (usually corticosteroid or antibiotic) has been used to define as an exacerbation "in an operative way" in clinical studies or in the data in the database (2, 3). The diagnosis of AECOPD remains a clinical diagnosis. The reporting of symptoms by the patients and the interpretation by the medical doctor can be prone to subjective, unstable evaluation, suggesting the need for more objective criteria for the disease activity. The difference of symptom variation from day to day from symptoms as a consequence of the exacerbation manifesting, remains a clinical challenge. Thus, the use of laboratory parameters in order to to improve the diagnostic accuracy of AECOPD is a field of continuous interest (4).

MATERIAL AND METHODS

There is a prospective observational study conducted on Regional Hospital Fier, in order to study clinical-laboratoric characteristics of patients affected by COPD exacerbations. 56 patients with COPD stages III and IV in a state of exacerbation are enrolled in this study . data are collected according to the protocol as well as the anamestic clinical and laboratic examinations.. At the first consultation, for reasons of COPD exacerbations and after 21 days, CRP, IL 6, PARC/CCL18, cellular content of sputum and blood has been defined.

STATISTICAL ANALYSIS

All of the collected data were first presented in Microsoft-Excel and then they were exported in SPSS (Statistical Package for Social Sciences) 20.0 and Medstat. The statistical analysis was performed after the above mentioned process. For all cathegoric variables (nominal, including the binary, dychotomic scale and ordinal), the absolute values and respective percentages were calculated. For all numerical variables, in which the data was subjected to a normal spread, the mathematical averages ± respective standard deviations. The data was represented through simple and compound charts, as well as graphs. The values of $p \leq 0.05$ were considered significant.

RESULTS

In the studied group of 56 patients, suffering from AECOPD, most (41 cases-73.1%) are in the age group from 65 to 79, often (29 cases – 32.1%) in the age group 65-69 years old. In the study there is a predominance of male patients (54-96%) and more often of rural origin (32 – 57%), whereas according to profession, 30

(53.6%) are workers. In the patients enrolled in the study there have been registered 73 accomopanying diseases, cardiovasculary ones predominating (41 cases – 56.2%). Only 5 (8.9%) of the patients did not have data on accompanying diseased.

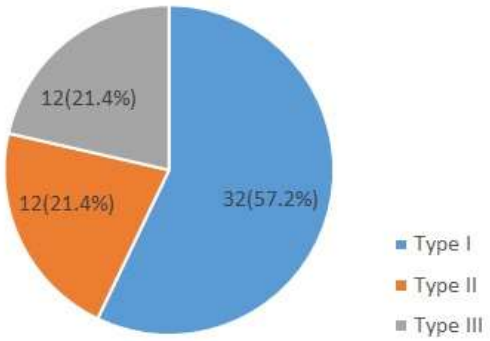
The predominating portion of the patients have been smokers; 21(37.5%) active smokers and 32 (57.1%) former smokers, with only 3(5.4%) being non-smokers.

According to patient references the appearance of cough has been in ≤4 years in 12 (21.4%) cases, 5-9 years -20(35.7%), 10-14 years -16(28.6%), 15-19 years -4(7.1%) and >19 years -4(7.1%). Theappearance of sputum has resulted with ≤ 4 year in 13(23.2%) cases, 5-9 years – 25(44.6%), 10-14 years -11(19.6%), 15-19 years – 3(5.4%) and >19 years -4(7.1%). The symptom of dyspnoea has been present for ≤ 4 years in 13 (23.2%) cases, 5-9 years -29(51.8%), 10-14 years -10 (17.6%), 15-19 years -2(3.6%) and >19 years -2(3.6%). The nature of sputum in 5(9%) of the patients has been mucous, in 37 (66%) – mucous-purulent and in 14 (25%) purulent.

All AECOPD patients manifested dyspnoea, an increase of sputum quantity (76.8%) and sputum purulent (58.9%). According to exacerbation types most of patients (57.2%) have been of type I.

According to Anthonisenexacerbation types 32 (57.2%) of the exacerbations have been of type I, 12 (21.4%) of type II, and 12 (21.4%) of type III (Fig.1).

Figure 1. Comparison of cellular structure in sputum in exacerbation and after 21 days



From the anamnesis, it results that patients taken into study, 14 (25%) have gone through one exacerbation per year, 31 (554%) -2 exacerbation per year, 9 (16.1%) -3 exacerbations per year and 2(3.6%) -4 exacerbations per year.

In AECOPD there has been an increase of sputum total cell count in 39 (69.6%), macrophage -55 (98.2%), neutrophils -51 (91.1%), lymphocytes -37 (66.1%), eosinophils -19(33.9%) and epithelial cells -9 (16.1%). Whereas after 21 days, the ones that have remained increased were, for total cell count in 13 (23.2%), totally normal or decreased macrophages, neutrophils -13 (23.2%), lymphocytes -45 (80%), eosinophils -6 (10.7%), and epithelial cells -26 (46.1%).

In the sputum of patients with COPD exacerbations according to stratification there has been eosinophilic sputum in 9 (16.1%), neutrophilic 16(28.6%) and paucigranulocitic 31(55.4%).Whereas after 21 days of the beginning of the exacerbation, total cells have remained increased in 12(23.2%), macrophages in totally normal or decrease, neutrophils

Table 1. Comparison of cellular structure in sputum in exacerbation and after 21 days

Cell structure in sputum	Means± Std. Deviation In exacerbation	Means± Std. Deviation after 21 days	Comparison of means (t-test)
Nr cells in sputum	14.4±4.51	8.71±3.52	P<0.0001
% eosinophils	.83±1.32	.28±.59	P<0.0001
% neutrophils	51.63±10.22	31.52±7.44	P<0.0001
% macrophages	33.13±7.12	43.03±7.98	P<0.0001
% lymphocytes	6.71±2.76	9.70±4.50	P<0.0001
% epithelial	7.45±3.73	10.34±3.91	P<0.0001

13(23.2%), lymphocytes -45(80%), eosinophils -6(10.7%) and epithelial cells 26(46.1%). The number of cells in sputum and their structure expressed in % has significant differences with the results after 21 days (P<0.0001). (Tab1)

The average initial blood leukocytosis was 11777± 5233, after 21 days in 8593±2630 (P<0.0001). AECOPD leukocyte formula (%) and after 21 days resulted respectively: rod nuclear 6.63±3.68 and 2.79±2.51 (P<0.0001), neutrophils -72.41±12.38 and 60.68±10.12 (P<0.0001), eosinophils-2.1±2.69 and 3.81±3.49 (P=0.0045), basophils -0.21±0.27 and 0.22±0.28 (P=0.8478), monocytes -8.15±4.53 and 7.49±3.15 (P=0.3727), lymphocytes -17.07±8.80 and -27.62±8.19 (P<0.0001). (Tab. 2)

The increased level of leucocytes in blood in AECOPD has been increased in 35(62.5%), sticks-26(46.4%), neutrophils -28(50%), eosinophils -7(12.5%), basophiles -1(1.8%), monocytes -21(37.5%) and lymphocytes -1(1.8%). Whereas after 21 days the level of leucocytes has continued to be increased in 5(8.9%), in sticks -1(1.8%), eosinophils -13(23%), neutrophils and basophiles – none, monocytes -16(28.6%) and lymphocytes -3(5.4%).

NRL at AECOPD and after 21 days resulted respectively 7.464±12.922 (from 1.04 to 97.9) and 2.509±1.18 (from 0.71 to 7.09) (p= 0.004). (Fig. 2)

Table 2. Comparison of leukocitary element % in exacerbation and after 21 days

Leukocitary blood formula	Means± Std. Deviation In exacerbation	Means± Std. Deviation After 21 days	Comparison of means (t-test)
Nr of leucocytes	11.777±5.233	8.593±2.630	P<0.0001
% Sticks	6.63±3.68	2.79±2.51	P<0.0001
% Neutrophils	72.41±12.38	60.68±10.12	P<0.0001
% Eosinophils	2.1±2.69	3.81±3.49	P=0.0045
% Basophils	.21±.27	.22±.28	P=0.8478
% Monocytes	8.15±4.53	7.49± 3.15	P=0.3727
% Lymphocytes	17.07±8.80	27.62±8.19	P<0.0001

Figure 2. NRL at AECOPD first consultation and after 21 days.

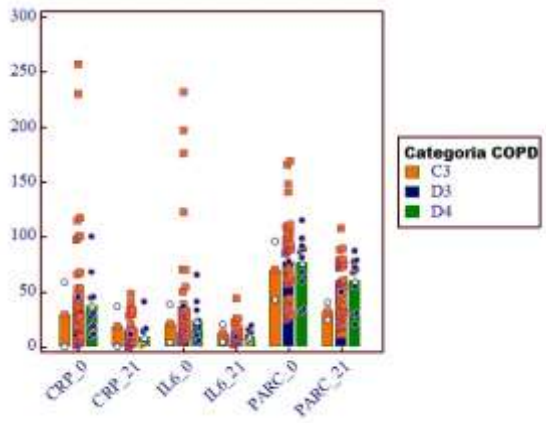
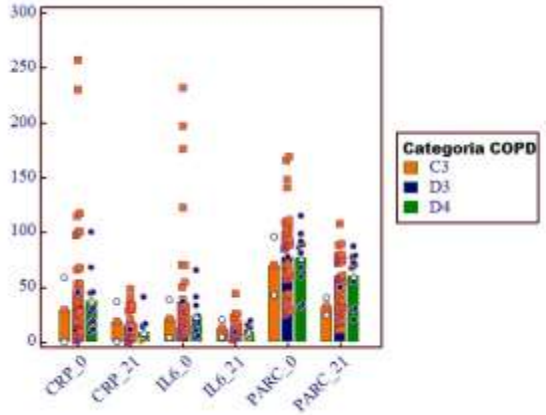


Figure 3. Biomarker levels by COPD category



There are no normal CRP values in category D4 cases and greater values of the level from 40 to over 200 mg/l are in relations to categories D3 and D4. In the results of examinations after 21 days, it is noted that cases are collected in CRP levels below 40 mg/l. AECOPD IL6 values of >7pg/ml are grouped in categories D3 and D4, whereas in the examination after 21 days, a drop in the frequency of the levels >7pg/ml is observed. AECOPD PARC values >30ng/ml are 91.1% of cases, whereas in values >60 ng/ml are 66.1% of cases. In the examination after 21 days of PARC it results that the value of >30ng/ml is in 71.4% of cases, whereas in values >60ng/ml, are 37.5% of cases. (Fig. 3)

DISCUSSION

Analised AECOPD patients have been predominant in the age from 65 to 79 (41 cases-73.1%), often in the ages 65-69 years (29 cases -32.1%). Males predominate (54 -96%) and more often those of rural origin (32 -57%), whereas by profession 30 (53.6%) are workers. This is in accordance to many studies on how males predonimate on AECOPD, which is related to smoking as well. Furthermore, in studies, to identify risk factors on exacerbations and hospitaliations of COPD, a more advanced age has been identified as a risk factor. (5, 6)

Regarding the influence of sex in COPD, there are contrasting opinions, where the actual data suggests different risk of COPD for different communities. Amidst different possible explanations observed among sexes, there are differences in pulmonary morphology, fumation, hormonal factors, the difference between genderin inflammatory reaction and professional factor interveners. (7)

In the study of 56 patients, it appears to have been registered 73 accompanying diseases, cardiovascular ones predominating (41 cases -56.2%). Only 5(8.9%) of the diseased did not have data for accompanying diseased; 8(11.4%) were afflicted with two accompanying diseases and 7(12.6%) with three accompanying diseases. As a result of the aging of the population and the fact that some chronic diseases have common

risk factors; the concomitants diseases are more common in COPD patients. (8) Consequently the management of patients with complex concomitants diseases, which has been formerly a field of geriatrics, has become a problem for most medics, that handle treatment of pulmonary diseases. The concomitants disease has to be distinct from the base disease, in this case, COPD exacerbations.

Concerning the data on the family anamnesis, there have been 6 (10.7%) patients with COPD data in their family and 3(5.4%) for pulmonary diseases, where in 6(10.7%) cases, it was the father, in 2(3.6%) the brother and in 1(1.8%) the mother, whereas in the male sex, a cofactor was the use of tobacco. There have been studies to determine whether family ancestry has anamnestic data for COPD as well as to determine whether ancestral predisposition is connected to the habit of smoking, increases the likelihood of COPD in comparison with other risk factors, mentioned separately. The conclusion is that in ancestors known for COPD, lays a significant risk factor for its development. Ancestors known for COPD and smoking, increase the likelihood of COPD development in comparison to the risk factor taken separately. (9)

Smoking is the only environmental risk factor the contribution of which in COPD is undisputed. Even though the relation between fumation is well defined, there are still some unclear matters in the correlation, including the basis with a wide variation in relation to the sensitivity to tobacco smoke, within and in between populations.The predominating portion of the patients have been smokers; 21(37.5%) active smokers and 32 (57.1%) former smokers, with only 3(5.4%) being non smokers. Interventions that decrease the risk of hospitalisation for COPD patients include cessation of smoking. (10)

The mucus hypersecretion has been moderated with the asthma pathogenesis, whereas in the bronchitis pathogenesis it is the predominating factor. Main COPD symptoms are dyspnea in effort, cough and sputum. (11) Other present symptoms, even if presumed not to be as important, include wheezing and toracal discomfort. Edemas in the feet speak for right heart disfunction and is an indicator of gravity. (20)

Many researchers in the years 1970 and 1980 considered coughing and sputum as the most important characteristics of the COPD exacerbation even if many of these studies tried to determine the contribution of viruses in COPD exacerbations. Even then, by Anthonisen and beyond, dyspnea was considered a key symptom of the exacerbations.

Biological markers of COPD exacerbations are very varying and it is difficult to predict the impending beginning of an exacerbation. Changes in the pulmonary function immediately before the exacerbation are small and not too useful in predicting worsening of COPD symptoms. In fact, the decrease of PEFR or FEV1 are also of little sensitivity on the

discovery of the beginning of the exacerbation, even when these two parameters are measued daily. AllAECOPD patients have manifested dyspnea. Dyspnoea is a common and worrying manifestation in patients with COPD and itsrelief is an important purpose of therapy.

The studies of bronchial inflammation in COPD have presented contradictory results. The mixed picture reflects the heterogeneity of the exacerbations, and partially explains their variability, different in reaction, to inhalatory steroids in COPD exacerbations (12) Characteristic inflammatory differences, with high levels of macrophages and lymphocytes, are evidenced in the pulmonary pathways of the smokers. These are more pronounced in patients with COPD and represent a normal exaggerated reaction to the inhaled toxins. The cellular inflammatory model differs in the stable and exacerbated state of asthma and COPD. Eosinophilic inflammation is classically connected to asthma (13, 14) and is the predominating cellular type in all forms of asthma. Even so, neutrophilic based inflammation is identified in the bronchial pathways in the more severe asthmatic forms (15) and this predominates during the exacerbation.It is suggested that this more severe group, with a prevalence of neutrophils reacts less to traditional therapy with inhalatory corticosteroid, than those with eosinophilic inflammation. Neutrophils and macrophages predominate in COPD and their levels increase with the level of disease gravity, and furthermore during the exacerbation. This is in contrast to asthma, where the macrophages aren't thought to play a part. A difference with the presence of neutrophils, eosinophils in sputum are increased in a significant way only in exacerbations of subgroups caused by viral infections.Eosinophilia and a lack of neutrophils in sputum can be an indicator of viral infection during COPD exacerbation. Eosinophilic inflammation generally is not related to COPD. In a stable state there is little proof of the role of eosinophils, except in a COPD defined phenotype, that shows little pronounced emphysema and with a thickening of bronchial walls in CT and a good reaction to corticosteroids. (16) This phenotype of COPD has many characteristics of asthma and would be interesting to compare bronchial tissue histology from the patients with this particular phenotype of COPD and that of asthma patients. During COPD exacerbations it is known that an inflammatory picture "akin to that of asthma" could exist, in the bronchial pathways with an increased number of eosinophils(17). According to our data data it results that at the time of the resolution of the exacerbation, there is a drop in the number of neutrophils, which is related with the uprooting of bacteria from sputum. Smokers with stable COPD have an increased number of macrophages in the bronchial tissue in comparison with patients with chronic bronchitis, but without bronchial obstruction or the healthy control group. During COPD exacerbations, observing studies have not shown

a significant increase of macrophages in sputum or bronchial tissue, neither as a percentage of the cell total, neither as an absolute increase of cells (18). In thisa study there is a different result – an increase of macrophages in the exacerbation. With the improvement of the exacerbation there is a significant decrease in the number of leucocytes, mainly as a consequence of the decline in neutrophils(19). The number of neutrophils in blood, increased in the systemic inflammation. The increased number of neutrophils is connected with the progression of COPD (20). Our data matches the data from the studies where the level of the leucocytes has resulted with a very significant increase, in patients with a COPD exacerbation in comparison with the patients in remission.

A high number of leucocytes do not necessarily indicate an infection; the number of leucocytes can be increased due to physiological stress, the use of steroids or beta-agonists (21). An indicator used in the evaluation of inflammation in COPD is the rapport of the blood formula elements –neutrophil/lymphocyte (NLR). The valour of NLR of patients with exacerbated or stable COPD is found to be considerably higher than those of the control group (21) .The number of leucocytes and the elements of the leucocitary formula are known as markers of inflammation(22). Due to the physiological reaction of the leucocytes in the blood to the stressing factors is increasing in the number of neutrophils and in decline in the number of lymphocytes, the rapport of these two elements with one-another having been used in clinical practice (23).

In general, as it can be observed observed and in this study, the levels of NLR have resulted higher in patients with stable COPD and in AECOPD patients, in comparison to the healthy control group and correlate with the traditional inflammation markers. Our results suggest that, in accordance with present information, that the NLR can be considered a reliable and simple marker in the definition of inflammation increase in patients with COPD. Furthermore, NLR can be useful for the early discovery of possible acute exacerbations in COPD patients 21.

According to present information, a quick, specific test to determine the bacterial infections of the lower respiratory pathways insures a great improvement in the plane of management. C-reactive protein hasn't been satisfactory as it belongs to sensibility and specificity (24). Procalcitonin, which does not increase either in the autoimmune inflammation and neither from a singular viral infection, has given more encouraging results (25).

The CRP levels have resulted higher in COPD patients in a state of exacerbation in comparison to those with stable COPD. It is known, that the most common cause of exacerbation in COPD patients is infection. In patients in a state of exacerbations, CRP values can be significantly higher depending on the infections. Even so, high CRP levels even in patients with stable COPD suggest systemic inflammation in these

patients (20). It has been reported that IL-6 concentration is higher in peripheral blood of COPD patients and represents a credible marker of discriminative systemic inflammations, amidst COPD patients and smokers without COPD. (26) Few studies have evaluated PARC/CCL-18 as a biomarker for COPD. Increased serum levels of CCL-18 correlate with mMRC and high values of CAT (27).

A high NLR can be used as a marker, similar to CRP, leucocytes and ESR, in the definition of inflammation increase in COPD exacerbations. NLR can be useful for the early discovery of potential acute exacerbations in COPD patients, who have normal levels of traditional markers(24).

In relations to categories of COPD resulted that CRP, IL6, and PARC have significantly higher levels in categories D3 and D4.

CONCLUSIONS

-In COPD exacerbations, patients of an advanced age and male sex predominate, with concomitant diseases, with a predomination of cardiovascular ones.

-Mucous-purulent and purulent sputum has predominated, and all patients have shown an increase of dyspnea.

-Patients have in most cases been of type I exacerbations according to Anthonisen.

-Clinical symptoms and biologic markerscan evaluate COPD exacerbations and its return to a stable state.

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