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# The Prevalence and Risk Factors of Cardiovascular Comorbidity in Patients with Severe and Very Severe COPD

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## Abstract

Cardiovascular comorbidities are most frequent comorbidities in COPD and are responsible for many deaths in those patients. The aim of the study was to investigate the prevalence and the risk factors of these comorbidities. In the survey 114COPD patients were included with severe and very severe stage of the disease, FEV1<50

***Index terms***— severe COPD, very severe COPD, risk factors, cardiovascular comorbidity.

I. Introduction hronic obstructive pulmonary disease (COPD) is defined as a systemic disease, and is a major cause of morbidity and mortality throughout the world and continues to cause a heavy health and pathophysiology of COPD, focused on the concept of systemic inflammation, has also helped to explain the high comorbidities frequency in these patients. Comorbidities affect seriously health status and influence the prognosis of these patients (1, **??**). Cardiovascular comorbidities are responsible for many deaths in COPD patients. The risk of cardiovascular morbidity and mortality is two to three times higher in patients with COPD in comparison to an age-matched and gender-matched population without COPD. (1,4,5) Probably due to shared pathophysiological mechanisms; cardiovascular comorbidities often remain unrecognized in patients with COPD. Great number of severe even very severe cases of COPD first has been diagnosed in the Cardiovascular Intensive Care Units during myocardial infarction or some other cardiovascular disease. (6,7,8) Longitudinal population-based studies show that low lung function, measured by forced expiratory volume in 1 second (FEV1), is associated with cardiovascular mortality. Participants in the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study with the lowest levels of FEV1 showed 5 times higher risk of deathby ischemic heart disease. (9,10,11) In recent years, a hypothesis has been generated that a systemic inflammatory process, present in COPD patients, could be the link between this disease and different comorbidities. Inflammatory cytokines, including tumor necrosis factor-?, interleukin-6, C-reactive protein (CRP) and fibrinogen, are increased within the circulation of patients with COPD, particularly during exacerbation when this inflammation significantly increase, probably representing an overspill of inflammatory mediators from the peripheral lung. These cytokines are common to many inflammatory diseases, and could explain their association with COPD.(4,12.13,)Risk factors, however, can also explain this association. Tobacco is a most common risk factor implicated in the genesis of COPD, remain as well as cardiovascular disease. In addition, the reduced physical activity due to reduced exercise tolerance first of all as a result of dyspnea, which is a primary clinical feature of chronic obstructive pulmonary disease (COPD). (1,2,14,15) The increase of vascular disease can be due to the higher prevalence of classic risk factors. Thus, in the recently published Cardiovascular Risk Factors in COPD study (4), it was observed that COPD patients presented high prevalence of hypertension, diabetes, and dyslipidemia, which were related with an increased risk for ischemic heart disease.The pathophysiological mechanisms underlying the vascular alterations in COPD are mainly mediated by endothelial dysfunction and coagulopathy. The systemic inflammation observed in COPD seems to be the key determinant for the development of pulmonary and systemic endothelial dysfunction. (1)Low body mass index (BMI) and weight loss is common in many chronic diseases; however, in COPD the picture is more complex, as low weight is due to a disproportionate loss of fat-free tissue, especially muscle mass increase death risk. (15,16) The mechanisms explaining cachexia in COPD are still **??**6) but go beyond the classic explanation of an increase in the oxygen cost of breathing, or the proinflammatory

effect of hypoxemia. (16,17)Physical inactivity and smoking were more strongly associated with the presence of comorbidities compared with airflow obstruction. ( **??**7)

# 1 II. Material and Methods

The aim of the study was to investigate the prevalence and risk factors of cardiovascular comorbidities in privies diagnosed COPD patients with severe and very severe stage of the disease, which ware stable. For that we investigated 114 subjects, all of them current smokers, with smoking status >10 years. According Global Initiative for Chronic Obstructive Lung Disease the patients with severe stage of the disease were with: 50% >FEV1>30%, FEV1/FVC <0,70, and with very severe stage of the disease: FEV1<30%, FEV1/FVC <0,70. Then they were divided in two groups: 92 subjects with and22 without cardiovascular comorbidities. It was cross sectional study. Besides demographic parameters (age, gender), body mass index (BMI), level of cholesterol, LDL and HDL, CRP, mMRC dyspnea scale, we use CAT score, according to the: 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document which recommends assessment of chronic obstructive pulmonary disease (COPD) using symptoms and future exacerbation risk, employing two score cut-points: COPD Assessment Test (CAT) score ?10 or modified Medical Research Council dyspnea scale (mMRC) grade ?2, and exacerbations number (18,19). Also the number of exacerbations and number of cardiovascular comorbidities were calculated.

# 2 a) Statistical analysis

Statistical analysis: Statistical analysis of the data base was made in the program SPSS for Windows 17, 0.Testing of the distribution of the data was done with Kolmogorov-Smirnov and Shapiro-Wilk's test. Categorical variables were presented with absolute and relative numbers, numeric variables were shown MPC descriptive statistics (mean, median, rank values).For comparing of respondentswith and without cardiovascular comorbidities were used parametric and nonparametric methods for independent samples(Chisquare test, Student t-test, Mann-Whitney U test). The correlation between the number of cardiovascular comorbidities and both (mMCR dyspnea scale and CAT test) was analyzed with Spearman-s a duty-rank correlation. For independent significant factors ?ssociated with cardiovascular comorbidity,Binary Logistic Regression analysis was used. For statistically significant values was taken p<0,05.

# 3 III. Results

In the research participated 114 subjects, COPD patients. Cardiovascular comorbidity was detected in 92 (80.7%) respondents, 61.9 % with severe and 38.1 % with very severe COPD.

Sex, age and body mass index of patients with severe and very severe HOBB had not significant effect on the occurrence of cardiovascular comorbidity ( c p=0.9, ? p=0.98 and p=0.19 consequently) The values of cholesterol, LDL and HDL insignificantly differ between patients studied with and without cardiovascular comorbidity.

Elevated blood sugar significantly more often was registered in the group of patients with cardiovascular comorbidity compared with patients without cardiovascular comorbidity (25% vs 0%).

In group with cardiovascular comorbidity were measured significantly higher values of glucose (p = 0.023). More than 50% of subjects with cardiovascular comorbidity present or 54.35% had values of CRP higher than 6 mg/l. Significantly higher values of CRP were observed in the group of patients with cardiovascular comorbidities (p = 0.00007). Respondents with and without cardiovascular comorbidity scores had insignificantly different mMRC, while significantly differed in terms of CAT score (p <0.0006). CAT average score in the group, with and without cardiovascular comorbidity was 9.56 ± 0.5 and 15.54 ± 5.0 consequently), while the median score was 10 (range 9-100 ) and 17 (range 10-20 ) consequently.

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Values of CAT score higher than 10 were significantly more likely registered only in group with cardiovascular comorbidities (67.39 %).

COPD pacients with and without cardiovascular comorbidity significantly differ in the number of exacerbationsin addition to patients with cardiovascular comorbidity (p <0.0001). Patients with CRP values greater than 6 mg/l were more significant in the register group 3 or 4 cardiovascular comorbidities as compared with the group with one or two cardiovascular comorbidities (88.46 % vs. 42.42% p = 0.00006).

CAT score significantly differed in patients with different number of cardiovascular disease (p<0.0001). The number of cardiovascular comorbidities in patients with severe and very severe COPD significantly positively correlated with mMRC and CAT scor (R = 0.423 and R = 0.637 accordingly ) Fig. **??** and Fig. **??**. Fig. **??** Fig. **??** IV. Discussion COPD is primarily characterized by the presence of airflow limitation resulting from inflammation and remodeling of small airways and is often associated with lung parenchymal destruction or emphysema. It is increasingly recognized that COPD extends beyond the lung and that many patients have several systemic manifestations that can further destruction or emphysema. It is increasingly impair functional capacity and health-related quality of life [11,20,21]. In addition, COPD is associated with several other diseases.

Rover L. in a systematic literature review concluded that FEV1 is a risk factor for cardiovascular mortality in patients of COPD, 10% decrease in FEV1 increases all-cause mortality by 14%, cardiovascular mortality by 28%, and nonfatal coronary event by almost 20%. (22) The leading causes of hospitalizations and mortality among

COPD patients are cardiovascular events. In the Lung Health Study, over 5 800 patients with mild to moderate COPD were studied. Forty-two to 48% of all hospitalizations that occurred over the study's 5-year follow-up period were related to cardiovascular complications.

Various population-based studies suggest that independent of smoking, age, and gender, COPD increases the risk of cardiovascular morbidity and mortality twofold. (11) In our survey from 114 COPD patients which were included, 92 (80,7%) had cardiovascular comorbidity. Sex, age and body mass index of patients with severe and very severe HOBB had not significant effect on the occurrence of these comorbidity (p=0.9, p=0.98 and p=0. 19).

It is very alarmingly that the use of bronchodilators, which are commonly used to treat symptoms in COPD, may increase the risk of cardiovascular morbidity and even mortality among COPD patients. Some dates discuss the epidemiologic evidence linking COPD and cardiovascular events as well as the potential mechanism(s) which may be responsible for this association. A pooled analysis of similar longitudinal studies determined that for every 1, it increased to 2.2(95% CI 1.9-2.5) for those in GOLD 2, and 2.4(95% CI 1.9-3.0) in GOLD spirometry stage 3-4. (6,9,24) Chen et al. identified 18,176 unique references and included 29 datasets in the meta-analyses. Compared with the non-COPD population, patients with COPD were more likely to be diagnosed with cardiovascular disease (odds ratio [OR] 2?46; 95% CI 2?02-3?00; p<0?0001), including a two to five times higher risk of ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries. Additionally, patients with COPD reported hypertension more often (OR 1?33, 95% CI 1?13-1?56; p=0?0007), diabetes (1?36, 1?21-1?53; p<0?0001], and ever smoking (4?25, 3?23-5?60; p<0?0001). The associations between COPD and these cardiovascular disease types and cardiovascular disease risk factors were consistent and valid across studies. (21,24)Metabolic syndrome also is one of the comorbidity in COPD patients. It is one of the risk factor for cardiovascular comorbidity. (25,26,27,28) In our group of patients the values of cholesterol, LDL and HDL insignificantly differ between patientswith and without cardiovascular comorbidity, butin this group were measured significantly higher values of glucose (p = 0.023).

Systemic inflammation that occurs in COPD is considered one of main risk factors for cardiovascular comorbidities in these patients. (30,31)The chronic inflammatory process in the lung contributes to the extrapulmonary manifestations of COPD which are predominantly cardiovascular in nature. Same dates review the significant burden of cardiovascular disease in COPD and discuss the clinical and pathological links between acute exacerbations of COPD and cardiovascular disease. The exacerbations increase the inflammation. (29) CAT test (25,26,27) is designed as a simple tool to assist patient's health status, and for identification of patientsat increased risk of exacerbations. (32,33) More than 50% of subjects in our survey with cardiovascular comorbidity is present or 54.35% had values of CRP higher than 6 mg/l. Significantly higher values of CRP were observed in the group of patients with cardiovascular comorbidities (p = 0.00007).And as an independent predictor of cardiovascular comorbidity regression analysis confirmed serum marker CRP (p = 0.013). Alsoour pacients with and without cardiovascular comorbidity significantly differ in the number of exacerbations in addition to patients with cardiovascular comorbidity (p <0.0001).The number of cardiovascular comorbidities in patients with severe and very severe COPD significantly positively correlated with mMRC and CAT scor (R = 0.423 and R = 0.637 accordingly). Values of CAT score higher than 10 were significantly more likely registered only in group with cardiovascular comorbidities (67.39 %).

# 5 V. Conclusion

Chronic obstructive pulmonary disease (COPD) is a growing global epidemic that is particularly important in developing countries. Comorbidities, especially cardiovascular are frequent occurrence in these patients, and significantly influence the treatments and prognosis of the disease. [1] [2]

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[2] The Prevalence and Risk Factors of Cardiovascular Comorbidity in Patients with Severe and Very Severe COPD


Figure 1: F

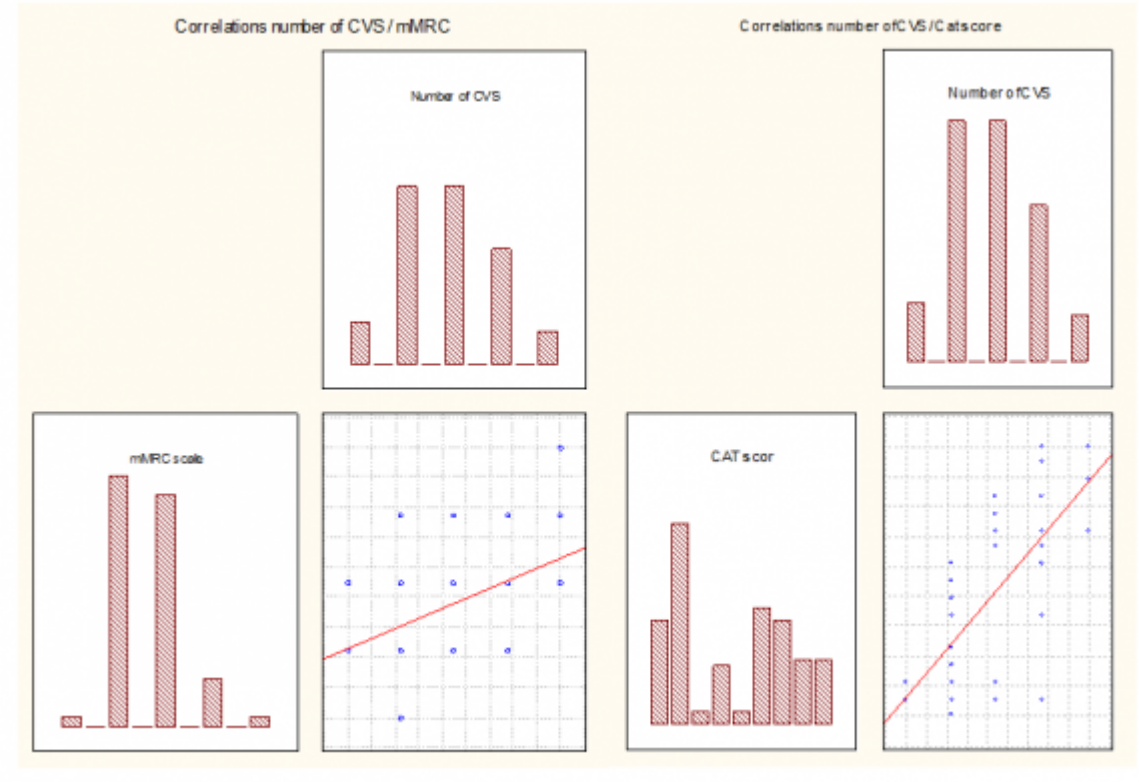


Figure 2:

**1**

| variable | noCVS N=22 | yesCVS N=92 | p value |
|---|---|---|---|
| gendern (%) | | | |
| Female 40 | 8 (20) | 32 (80) | c p=0.9 |
| Male 74 | 14 (18.92) | 60 (81.08) | |
| age (mean±SD) | | | |
| | 62,44 ± 6,4 | 62,34 ± 10,7 | ? p=0.98 |
| BMI (mean±SD) | | | |
| | 22.4 ± 6.6 | 24.87 ± 5.3 | ? p=0.19 |

*[Note: a (Student-ov t test) c (Chi-square)]*

Figure 3: Table 1 :

**2**

| variable | noCVS N=22 | yasCVS N=92 | p value |
|---|---|---|---|
| cholesteroln (%) | | | |
| 0 -5.51 | 14 (63.64) | 41 (44.56) | c p=0.1 |
| > 5.51 | 8 (36.36) | 51 (55.44) | |
| cholesterol | (mean±SD) median (IQR) | | |
| | 5.74 ± 1.2 | 6.17 ± 1.5 | b p=0.51 |
| | 5.6 (4.7 -6.6) | 5.6 (4.9 -6.1) | |
| LDL n (%) | | | |
| 0 -2.2 | 5 (22.73) | 24 (26.09) | c p=0.89 |
| 2.3 -3.7 | 11 (50) | 36 (39.13) | |
| > 3.7 | 6 (27.27) | 32 (34.78) | |
| LDL (mean±SD) median (IQR) | | | |
| | 3.13 ± 1.4 | 3.58 ± 1.1 | b p=0.21 |
| | 2.7 (1.9 -4.2) | 3.8 (2.2 -3.9) | |
| HDL n (%) | | | |
| 0.9 -2 | 6 (27.27) | 45 (48.91) | c p=0.09 |
| > 2 | 6 (27.27) | 11 (11.96) | |
| < 0.9 | 10 (45.45) | 36 (39.13) | |
| HDL (mean±SD) median (IQR) | | | |
| | 1.26 ± 0.7 | 1.25 ± 0.6 | b p=0.94 |
| | 1.2 (0.8 -2.1) | 1.2 (0.7 -1.8) | |
| glycemia n (%) | | | |
| 3.5 -6.1 | 22 (100) | 69 (75) | c p=0.02 |
| > 6.1 | 0 | 23 (25) | |
| glycemia (mean±SD) median (IQR) | | | |
| | 5.09 ± 0.4 | 6.44 ± 2.5 | b p=0.023* |
| | 5 (4.9 -5) | 5.7 (5 -6.4) | |
| CRP n (%) | | | |
| < 6 | 22 (100) | 42 (45.65) | c p=0.00004** |
| > 6 | 0 | 50 (54.35) | |
| CRP (mean±SD) median (IQR) | | | |
| | 4.22 ± 0.4 | 7.15 ± 2.8 | b p=0.00007** |
| | 4 (4 -4) | 7 (5 -9) | |

*[Note: b (Mann-Whitney test) c (Chi-square) *p<0.05 **p<0.01]*

Figure 4: Table 2 :

**3**

| variable | noCVS | yesCVS | p value |
|---|---|---|---|
| | N=22 | N=92 | |
| mMRC n (%) | | | |
| 1 | 0 | 2 (2.17) | b p=0.09 |
| 2 | 17 (77.27) | 40 (43.48) | |
| 3 | 5 (22.73) | 40 (43.48) | |
| 4 | 0 | 8 (8.69) | |
| 5 | 0 | 2 (2.17) | |
| CAT n (%) | | | |
| < 10 | 22 (100) | 30 (32.61) | c p<0.0001 |
| > 10 | 0 | 62 (67.39) | |
| CAT (mean±SD) median (IQR) | | | |
| | 9.56 ± 0.5 | 15.54 ± 5.0 | b p=0.0006** |
| | 10 (9 -100) | 17 (10 -20) | |
| egzacerbation number n (%) | | | |
| 0 | 9 (40.91) | 2 (2.17) | |
| 1 | 10 (45.45) | 33 (35.87) | |
| 2 | 3 (13.64) | 17 (18.48) | |
| 3 | 0 | 25 (27.17) | |
| 4 | 0 | 9 (9.78) | |
| 5 | 0 | 6 (6.52) | |
| egzacerbation number n (%) | | | |
| 0 | 9 (40.91) | 2 (2.17) | c p<0.0001 |
| 1-2 | 13 (59.09) | 50 (54.35) | |
| 2> | 0 | 40 (43.48) | |

b (Mann-Whitney test) c (Chi-square) *p<0.05 **p<0.01

As an independent predictor of cardiovascular comorbidity regression analysis confirmed serum marker CRP (p = 0.013). Increasing the values of CRP in serum 1mg/l in patients with severe and very COPD increases chance to 7.92 (95 % CI 1.545 - 14.607) times for cardiovascular comorbidity.

Figure 5: Table 3 :

**4**

| | | | | and very severe HOBB | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B | S.E | Wald | df | Sig. | Exp(B) | 95,0% C.I. for EXP | |
| | | | | | | | | Lower | Uppe |
| Step glycaemia | | 1,028 | 1,053 | ,952 | 1 | ,329 | 2,794 | ,355 | 22,00 |
| 1 a | CRP | 2,069 | ,834 | 6,158 | 1 | ,013 | 7,920 | 1,545 | 14,60 |
| | CAT | 1,661 | ,986 | 2,837 | 1 | ,092 | 5,267 | ,762 | 36,40 |
| | Constant | -30,152 | 12,614 | 5,713 | 1 | ,017 | ,000 | | |

a. Variable(s) entered on step 1: glikemijam CRP, CAT.

Figure 6: Table 4 :

**5**

| variable | number of CVS (1-2) | number of CVS (3-4) | p value |
|---|---|---|---|
| | N=66 | N=26 | |
| CRPn (%) | | | |
| < 6 | 38 (57.57) | 3 (11.54) | |

Figure 7: Table 5 :

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Figure 8:

[] , 10.1183/09059180.00008612.

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