Global Journal of Medical Research: F
Diseases
Volume 16 Issue 4 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

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

By Jagoda Stojkovikj, Beti Ivanovska-Zafirovska, Irina Angelovska, Angela Debreslioska, Sead Zejnel, Smiljko Jovanovski, Dragana Stojkovikj, Sasha Anastasova & Ivana Jovanovska

University Clinic of Pulmollogy and Allergology

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%, which were stable. Cardiovascular comorbidity was detected in 92 (80.7%) respondents, 61.9 % with severe and 38.1 % with very severe COPD. Blood sugar (p=0.023*), CRP (p=0.00007**), CAT score (p<0.0006**) and number of exacerbations (p<0.0001) were significantly higher in patients with cardiovascular comorbidity. We can conclude that cardiovascular comorbidities are frequent in COPD patients with severe and very severe stage. They have a great impact in this patients.

Keywords: severe COPD, very severe COPD, risk factors, cardiovascular comorbidity.

GJMR-F Classification : NLMC Code: QY 400

Strictly as per the compliance and regulations of:

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

Jagoda Stojkovikj [α], Beti Ivanovska-Zafirovska [σ], Irina Angelovska [ρ], Angela Debreslioska [ω], Sead Zejnel [¥], Smiljko Jovanovski [§], Dragana Stojkovikj [χ], Sasha Anastasova [ν] & Ivana Jovanovska [Θ]

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%, which were stable. Cardiovascular comorbidity was detected in 92 (80.7%) respondents, 61.9 % with severe and 38.1 % with very severe COPD. Blood sugar (p=0.023*), CRP (p=0.00007**), CAT score (p<0.0006**) and number of exacerbations (p<0.0001) were significantly higher in patients with cardiovascular comorbidity. We can conclude that cardiovascular comorbidities are frequent in COPD patients with severe and very severe stage. They have a great impact in this patients.**

Keywords: severe COPD, very severe COPD, risk factors, cardiovascular comorbidity.

I. Introduction

Chronic 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 economic burden. (1,2) Understanding of the 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 (1,3). 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-α, 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

Author α σ ρ ω ¥ § χ ν Θ : University Clinic of Pulmollogy and Allergology, Institute for Epidemiology and Biostatistics and Medical Informatics, University Clinic of Cardiology, Skopje, Macedonija.
e-mails: stojkovic_jagoda@yahoo.com, betizafirova@yahoo.com, irina.angelovska@yahoo.com, angela.debreslioska@gmail.com, sead.zeynel@gmail.com

unclear,(16) but go beyond the classic explanation of an increase in the oxygen cost of breathing, or the pro-inflammatory effect of hypoxemia. (16, 17)Physical inactivity and smoking were more strongly associated with the presence of comorbidities compared with airflow obstruction. (17)

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.

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(Chi-square 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 associated with cardiovascular comorbidity,Binary Logistic Regression analysis was used. For statistically significant values was taken p<0,05.

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, [a]p=0.98 and p=0.19 consequently)

Table 1 : The age, gender and BMI in patients

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	[a]p=0.98
BMI (mean±SD)			
	22.4 ± 6.6	24.87 ± 5.3	[a] p=0.19

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

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).

Table 2 : The level of cholesterol, LDL, HDL, glycaemia and CRP in patients

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)	

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

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.

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 ($p < 0.0001$).

Table 3 : The level of mMRC dyspnea scale, CAT test score and exacerbation number in patients

variable	noCVS N=22	yesCVS N=92	p value
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 10 (9 – 100)	15.54 ± 5.0 17 (10 – 20)	[b]p=0.0006**
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 severe COPD increases chance to 7.92 (95 % CI 1.545 - 14.607) times for cardiovascular comorbidity.

Table 4 : Binary Logistic Regression independent predictors of cardiovascular comorbidities in patients with severe and very severe HOBB

		B	S.E	Wald	df	Sig.	Exp(B)	95,0% C.I. for EXP (B)	
								Lower	Upper
Step 1[a]	glycaemia	1,028	1,053	,952	1	,329	2,794	,355	22,005
	CRP	2,069	,834	6,158	1	,013	7,920	1,545	14,607
	CAT	1,661	,986	2,837	1	,092	5,267	,762	36,401
	Constant	-30,152	12,614	5,713	1	,017	,000		

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

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).

Table 5 : The association of CRP and CAT score with number of comorbidities in patients

variable	number of CVS (1-2) N=66	number of CVS (3-4) N=26	p value
CRPn (%)			
< 6	38 (57.57)	3 (11.54)	[c]p=0.00006**
> 6	28 (42.42)	23 (88.46)	
CAT (mean±SD) median (IQR)			
	6.12± 1.7 6 (5 – 7)	9.61 ± 3.3 9 (8 – 11)	[b]p<0.0001**

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

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.1 and Fig.2.

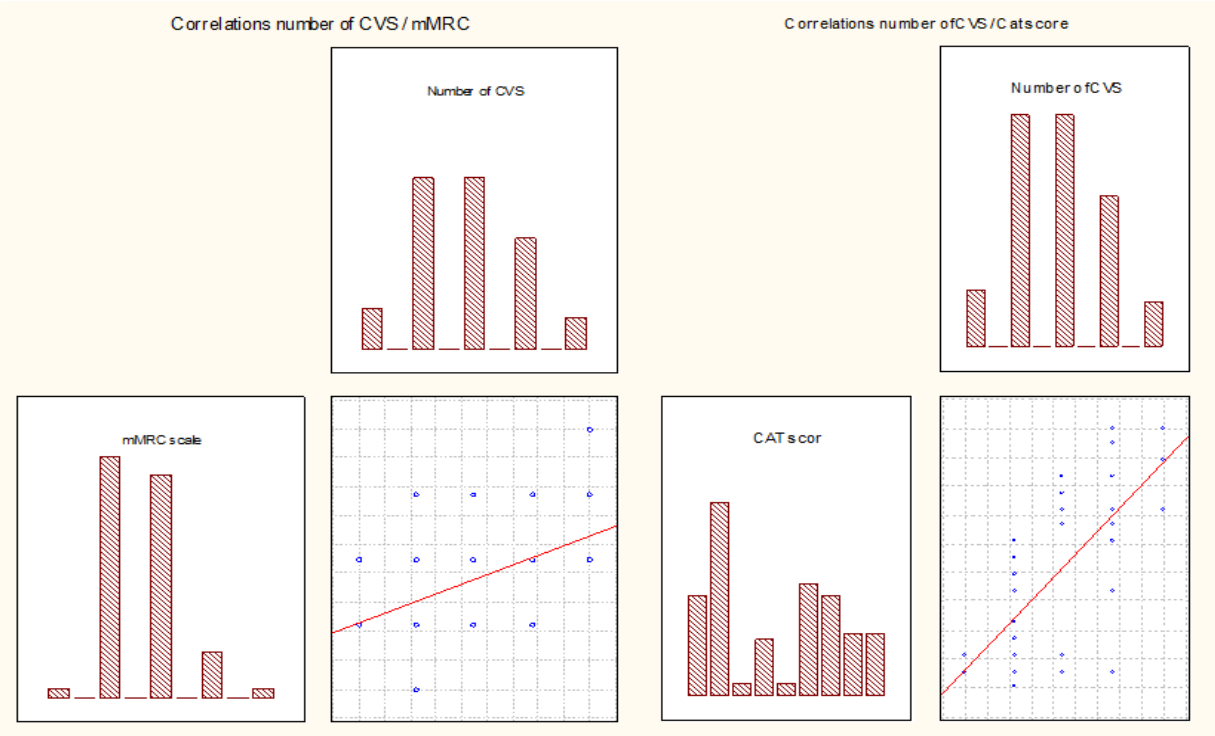

Fig. 1

Fig. 2

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 10% decline in FEV1, cardiovascular mortality increases by 28% showing a clear relation between overall cardiovascular death and low lung function.(9,23) A similar gradient exists if the analysis is limited to those fulfilling the diagnosis of COPD. Data from more than 5,000 participants in 2 cohorts (the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study) showed that while the odds ratio (OR) of having cardiovascular disease is 1.7 (95% confidence interval [CI] 1.5-1.9) for those in the Global Initiative for chronic Obstructive Lung Disease (GOLD) spirometry category

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 %).

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. Common risk factors in these patients are age, smoking, physical inactivity and systemic inflammation and treatment with corticosteroids. Lower FEV1-severe COPD, increases cardiovascular mortality and all-cause mortality.

References Références Referencias

1. Mannino, D.M. (2002).COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest, 121(5), pp.121–126. [CrossRef] [Medline]
2. Sidney, S. et al. (2005). COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest, 128, pp. 2068–2075. [CrossRef] [Medline]
3. Andriana, I. (2015). Cardiovascular comorbidities in hospitalised COPD patients: a determinant of future risk? European Respiratory Journal, 46, pp.846-849; DOI: 10.1183/09031936.00237014
4. Arnaud, C. et al. (2013). Comorbidities of COPD. European Respiratory Review, 22, pp. 454-475; DOI: 10.1183/09059180.00008612
5. Dionne, E. S. (2015). Impact of cardiovascular comorbidities on COPD Assessment Test (CAT) and its responsiveness to pulmonary rehabilitation in patients with moderate to very severe COPD: protocol of the Chance study. BMJ Open, 5(7), e007536.Published online 2015 Jul 21.doi: 10.1136/bmjopen-2014-007536PMCID: PMC4513521
6. Izquierdo, J.L. (2010). Lack of association of ischemic heart disease with COPD when taking into account classical cardiovascular risk factors.Int J Chron Obstruct Pulmon Dis, 8(5), pp. 387-94.PMID:21103405
7. Michael, F. (2012). Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study).Int J Chron Obstruct Pulmon Dis, 7, pp 679–686.doi: 10.2147/COPD.S36222PMCID: PMC3468057
8. VanDijk, W.D. et al. (2010).Interaction in COPD experiment (ICE): a hazardous combination of cigarette smoking and bronchodilation in chronic obstructive pulmonary disease. Med Hypotheses, 74(2), pp. 277-80. doi: 10.1016/j.mehy.2009.09.012. Epub 2009 Oct 1.
9. Sin, D.D. Man, S.F. (2005). Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease. Can J Physiol Pharmacol, 83(1), pp.8-13.

10. Sin, D.D. Man, S.F. (2008).Impact of cancers and cardiovascular diseases in chronic obstructive pulmonary disease. Curr Opin Pulm Med, 14(2), pp.115-21.doi: 10.1097/MCP.0b013e3282f45ffb.
11. Martinez, C.H. Miguel, D.J.Mannino, D.M. (2014). Defining COPD-related comorbidities, 2004-2014. J COPD F, 1(1), pp. 51-63. doi: http://dx.doi.org/10.15326/jcopdf.1.1.2014.0119.
12. Barnes, P. (2010). Chronic Obstructive Pulmonary Disease: Effects beyond the Lungs. PLoS Med 7(3): e1000220. doi:10.1371/journal.pmed.1000220
13. Sin, D.D. Man, S.F. (2005). Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality, Proc Am Thorac Soc, 2(1), pp. 8-11. doi: http://dx.doi.org/10.1513/pats.200404-032MS.
14. Mannino, D.M. (2008).Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. EurRespir J, 32(4),pp.962-969. doi: http://dx.doi.org/10.1183/09031936.00012408.
15. Langen, R.C. et al. (2013).Triggers and mechanisms of skeletal muscle wasting in chronic obstructive pulmonary disease. Int J Biochem Cell Biol, 45(10), pp. 2245-2256. doi: http://dx.doi.org/10.1016/j.biocel.2013.06.015.
16. Donahoe, M.et al. (1989).Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis, 140(2), pp. 385-391. doi: http://dx.doi.org/10.1164/ajrccm/140.2.385.
17. Li Wei, M.B.et al. (2004). Taking Glucocorticoids by Prescription Is Associated with Subsequent Cardiovascular Disease. Ann Intern Med. 2004, 141(10), pp. 764-770. doi: 10.7326/0003-4819-141-10-200411160-0000721.
18. Perez, T. et al. (2015). Modified Medical Research Council scale vs Baseline Dyspnea Index to evaluate dyspnea in chronic obstructive pulmonary disease. J Chron Obstruct Pulmon Dis. 2015, 10, 1663–1672. doi: 10.2147/COPD.S8240822.
19. Müllerová, H. (2014). Prevalence and Burden of Breathlessness in Patients with Chronic Obstructive Pulmonary Disease Managed in Primary Care. PLoS ONE. 9 (1), e85540. doi:10.1371/journal.pone.008554.
20. Van Remoortel1, H. et al. (2014).Risk Factors and Comorbidities in the Preclinical Stages of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 189(1), pp. 30-38. doi: 10.1164/rccm.201307-1240OC.
21. Chen, W. (2015). Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med. (8), pp.631-9. doi: 10.1016/S2213-2600(15)00241-6.
22. Roever, L. Resende, E.S. (2015). Cardiovascular Comorbidities in COPD Patients. Transl Med. pp.5, 151. doi:10.4172/2161-1025.1000151
23. Jones, P.W. et al. (2013).Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. European Respiratory Journal.42, pp. 647-654. DOI: 10.1183/09031936.00125612
24. Masaki, M. et al. (2014). Analysis of comorbid factors that increase the COPD assessment test scoresRespir Res. 15(1), pp.13. doi: 10.1186/1465-9921-15-13.
25. Leea,S.D. et al.(2014).The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. Respiratory Medicine. 108(4), pp. 600–608.
26. Jones,P.W. (2009).Development and first validation of the COPD Assessment Test. Eur Respir J. 34,pp. 648–654.
27. Sarioglua,N. et al. (2016).Is the COPD assessment test (CAT) effective in demonstrating the systemic inflammation and other components in COPD? ErelaRevista Portuguesa de Pneumologia (English Edition). 22(1), pp. 11–17.doi:10.1016/j.rppnen.2015.08.007
28. MacDonald, M. et al.(2016).Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. 4(2), pp.138–148.
29. Terzano, C. et al. (2010). Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. Lung. 188(4) pp. 321–329.
30. Man,S.F.P. et al.(2006). C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax. 61 (10), pp. 849–853.
31. Patil, S.P. J.et al. (2003). In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Archives of Internal Medicine. 163 (10). pp. 1180–1186.
32. Wong, A.W.M. et al. (2008). Acute exacerbation of chronic obstructive pulmonary disease: influence of social factors in determining length of hospital stay and readmission rates. Canadian Respiratory Journal. 15 (7) pp. 361–364.
33. Kessler, R. et al.(1999). Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 159(1), pp. 158–164.