COPD – Risk Factor for Complex Chronic Comorbidities, a Retrospective Case-Control Study

Hubatsch Mihaela[1], Kikeli P[1], Preg Z[1], László MI[2], Ene L[3], Germán-Salló Márta[1], Szentendrey Dalma[1], Bocicor Andrea[1]

[1] University of Medicine and Pharmacy Tirgu Mures, Romania
[2] Procardia Tirgu Mures, Romania
[3] County Clinical Hospital Tirgu Mures, Romania

Background: Increasing evidence indicates that chronic obstructive pulmonary disease (COPD) is a complex disease involving more than airflow obstruction. Systemic inflammation can initiate or worsen comorbid diseases, such as ischemic heart disease, heart failure, arrhythmia, diabetes, osteoporosis, lung cancer and depression.

Material and method: We explored the Medprax database, from an ambulatory care in order to obtain rates of comorbidities in COPD patients. Medprax electronic database is a locally developed system designed to fulfil the requirements of an integrated healthcare system. We identified a population of 9,659 patients (4472 men and 5187 women) aged ≥ 30 years registered between 01.01.2000 and 01.02.2010.

Results: The overall prevalence of COPD was 5.17% (384 men and 116 women). Compared to the non-COPD patients, COPD was found to be a significant risk factor in both sexes for cardiovascular events: ischemic heart disease (OR = 3.06, 95%CI 2.54–3.68), atrial fibrillation (OR = 2.70, 95%CI 2.12–3.43) and heart failure (OR = 4.49, 95%CI 3.74–5.40) regardless of age. Association with diabetes mellitus type 2 was extremely significant in COPD men (OR = 1.69, 95%CI 1.26–2.27), but not in COPD women. Significant correlation with osteoporosis (OR = 3.26, 95%CI 1.94–5.48) was found only in women over 60 years and men under 60. Pulmonary malignancy was found only in male COPD patient compared to non-COPD patients (OR = 5.04, 95%CI 2.02–12.44). The impact on depressive disorders was noted only in younger COPD men (OR = 5.71, 95%CI 1.94–16.82).

Conclusions: Our results indicate that COPD is a risk factor for all these comorbid conditions and that in the management of COPD all these conditions need to be carefully evaluated.

Keywords: chronic obstructive pulmonary disease, ischemic heart disease, heart failure, atrial fibrillation, diabetes mellitus type 2 , depression, lung cancer, osteoporosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating disease that causes significant morbidity and mortality worldwide, especially in the elderly. In the modern approach, there is a growing recognition that COPD is a respiratory disease with an important systemic component, with multiple organ dysfunctions because of the chronic inflammation. Furthermore, the comorbid diseases increase the morbidity and mortality of COPD, leading to additional hospitalisations and increase in healthcare costs [1].

In the most recent COPD definition by GOLD [2] it is stated that: "...symptoms, functional abnormalities and complications of COPD can partly be explained on the basis of this underlying inflammation of the lungs and the resulting pathology. These changes may also have significant extra-pulmonary or systemic consequences contributing to the severity in each individual patient".

COPD has systemic effects, and common co-morbid conditions such as cardiovascular disease (CVD), diabetes mellitus type 2 and osteoporosis may all be linked through a common systemic inflammatory cascade. [1] The term "chronic systemic inflammatory syndrome" has been proposed to define the inflammatory nature common to COPD and its comorbid conditions [2]. This proposition was based on the increasing body of evidence that systemic inflammation is related to the pathogenesis of CVD [3,4], metabolic syndrome [5,6] and COPD. Not fully reversible airflow obstruction has profound effects on cardiac function and gas exchange, with systemic consequences. In addition, as COPD results from inflammation and/or alterations in repair mechanisms, the "spill-over" of inflammatory mediators into the circulation may result in important systemic manifestations of the disease [7]. Regardless of the underlying mechanism, various studies indicate an association between COPD and the risk of cardiovascular diseases [8–10]. According to the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation, supraventricular arrhythmias are common in patients with COPD [11], and were frequently observed during exacerbations of COPD. Also, there are findings that metabolic syndrome was more common among people with advanced COPD, compared with age- and sex-matched controls [5]. Depression, anxiety and osteoporosis are also common in elderly COPD patients; these factors severely affect their quality of life [12]. COPD strongly correlates with lung cancer, it is an independent risk factor for malignant pulmonary neoplasm, while chronic bronchitis and/or emphysema increase lung cancer incidence risk by two- to fivefold as compared with smokers with normal spirometry [13].

The aim of the present study was to examine if COPD is supplemental risk factor for CVD and other important comorbidities in a large population-based sample from a multi-specialist ambulatory care in Romania between 2000 and 2010.

Methods

Data source

We explored the Medprax database to conduct a retrospective case-control study with a contingency table analysis in order to obtain rates of comorbidities in COPD patients. Medprax electronic database is locally developed software, designed to fulfil the requirements of an integrated healthcare system. It is a large database established in 1996, the developed software makes possible the acquirement and storage of all data from the primary, ambulatory and hospital care; allows data transfer between these levels of medical care; as well as enables complex analyses of the individual and population health status [14].

The doctors who contribute data to the Medprax database have been trained to record medical information in a standard manner. The recorded information includes demographics, patients' medical history and diagnoses, clinical and paraclinical findings, as well as all drug prescriptions. For this study we have used the electronic medical records from the specialist ambulatory care of Procardia, Targu Mures, Romania including data from the cardiology, internal medicine, pneumology ambulatories and one general practice.

Study population

We identified a population of 9659 patients (4472 men and 5187 women) registered in Medprax database between January 1, 2000 and February 1, 2010 and who were aged 30–89 years. From this population 500 were COPD patients, with a resulted non-COPD population of 9159 patients. We assessed and compared the prevalence of diagnosed CVD (ischemic heart disease, atrial fibrillation and heart failure), as well as other frequent comorbidities: diabetes mellitus type 2, osteoporosis, depression and malignant pulmonary neoplasm in the COPD group compared to the non-COPD population. All patients were identified using specific disease codes as recorded in the International Classification of Diseases (ICD-10).

Statistical analysis

In order to establish the existing or non-existing relation between the presence of COPD and the degree of comorbidities we measured the influence of the independent variable by the corresponding odds ratio (OR), with a confidence interval of 95% (95% CI). As the contingency tables included very large numbers, the InStat program automatically performed the chi-square test, even if one cell included numbers under 5 and the Fisher's test was selected. With smaller samples, the chi-square test is not so accurate and Yates' continuity correction was used. We estimated the odds ratio separately for each dependent variable for the total number of patients, but also compared the link between these parameters in relation to the age and sex distribution of the comorbidities in COPD and nonCOPD patients. The level of significance was determined by a p value less than 0.05. Statistical analyses were performed using the statistical software GraphPad InStat version 3.06 for Windows 95, GraphPad Software, San Diego California USA, www.graphpad.com.

Results

We identified a total of 9,659 patients registered in a specialist ambulatory care from Targu Mures, Romania between January 1, 2000 and February 1, 2010. The total studied population included slightly more women 5187 (53.70%) than men 4472 (46.30%), and 48.55% of the study population was 60 years of age or older at the time of the first recording of a COPD diagnosis. The overall prevalence of COPD was 5.17%, consisting of 500 patients of which 384 (76.80%) men and 116 women (23.20%), with a fourfold increase in men (9.39%) compared to women (2.28%). Characteristics of the study population are shown in Table I.

In order to evaluate the effect of COPD on the risk of developing the studied comorbities, we have calculated for every comorbidity the odds ratio, 95% confidence interval and P value for the total number of patients with or without COPD. But, as we know there are important differences between genders in the prevalence of COPD consequently we have also analysed the risk according to gender. We found that compared to the non-COPD patients, COPD was a significant risk factor in both sexes for cardiovascular events: ischemic heart disease (OR = 3.06, 95%CI 2.54 to 3.68, P value < 0.0001 considered extremely significant), atrial fibrillation (OR = 2.70, 95%CI 2.12 to 3.43 P value < 0.0001) and heart failure (OR = 4.49, 95%CI 3.74 to 5.40 P value < 0.0001). Association with diabetes mellitus type 2 was extremely significant (P value < 0.0001) in COPD men (OR = 1.69, 95%CI 1.83

Table I. Characteristics of the study population

	COPD patients		nonCOPD patients	
	Case no.	%	Case no.	%
Male	384	76.80	4088	44.64
Female	116	23.20	5071	55.36
Age groups (years)				
30-59	66	13.20%	4969	51.45
60-89	434	86.80%	4690	48.55
Comorbidities				
Ischemic heart disease	296	59.20	2944	32.14
Atrial fibrillation	91	18.20	697	7.61
Heart failure	255	51.00	1721	18.79
Diabetes mellitus type 2	75	15.00	846	9.24
Osteoporosis	20	4.00	273	2.98
Lung cancer	7	1.40	28	0.30
Depression	13	2.60	371	4.05

Table II. Number of cases with comorbidities in patients with and without COPD, odds ratio, 95% confidence interval and P value calculated for total (T), as well as male (M) and female (F) subgroups

Comorbidity / Number of patients	COPD patients			nonCOPD patients			Odds ratio (OR)			95% confidence interval (CI)			P value		
	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F
Ischemic heart disease	296	228	68	2944	1276	1668	3.06	3.22	2.89	2.54–3.68	2.60–3.99	1.98– 4.20	< 0.0001	< 0.0001	< 0.0001
Atrial fibrillation	91	67	24	697	325	372	2.70	4.95	3.94	2.12–3.43	3.99–6.14	2.72–5.71	< 0.0001	< 0.0001	< 0.0001
Heart failure	255	198	57	1721	723	998	4.49	2.44	3.29	3.74–5.40	1.83–3.26	2.07–5.22	< 0.0001	< 0.0001	< 0.0001
Diabetes mellitus type 2	75	60	15	846	403	443	1.73	1.69	1.98	1.34–2.23	1.26–2.27	0.88–2.69	< 0.0001	< 0.0005	0.15
Osteoporosis	20	2	18	273	3	270	1.35	7.12	3.26	0.85–2.15	1.18–42.81	1.94–5.48	0.24	0.08	< 0.0001
Lung cancer	7	7	0	28	15	13	4.63	5.04	1.60	2.01–10.65	2.04–12.44	0.09–27.23	< 0.0003	< 0.0004	0.58
Depression	13	9	4	371	83	288	0.63	1.15	0.59	0.36–1.10	0.57–2.32	0.21–1.62	0.13	0.82	0.40

to 3.26), but apparently the prevalence of diabetes was not increased because of the presence of COPD in women. Significant correlation with osteoporosis (OR = 3.26, 95%CI 1.94 to 5.48, P value < 0.0001) was found only in women. Lung cancer was found only in male COPD patient with an extremely significant prevalence compared to non-COPD patients (RR = 5.04, 95%CI 2.02 to 12.44, P value < 0.0004). The overall impact of COPD on depressive disorders (2.60%) was not observed in comparison to the studied non COPD population (4.05%). The above mentioned findings are displayed in Table II.

Furthermore, as COPD and the studied comorbidities are common conditions in elderly patients, we assessed the risk of COPD in younger patients less than 60 years of age. Table 3 illustrates in which way COPD represents a risk factor not only globally but also in subgroups represented by the gender distribution and age categories, taking as a reference the limit of 60 years.

Table 3. Case-control analysis of the risk of various comorbidities stratified by the age and gender of the patients with and without COPD

The risk for ischemic heart disease (OR = 5.93, 95%CI 3.63–9.57) and heart failure (OR = 4.75, 95%CI 2.72–8.32) was found to be extremely significant in younger male COPD patients compared to the non-COPD patients. Heart failure correlated significantly with COPD in younger women as well (OR = 7.11, 95%CI 2.40–21.06). Association with type 2 diabetes was highly significant among men with COPD, irrespective of age (OR = 2.96, 95%CI 1.48–5.93). Significant correlation with osteoporosis was found only in men less than 60 and in women over 60 years. The occurrence of pulmonary malignancy in younger COPD patients was difficult to assess because of low number of cases. The impact of COPD on depressive disorders was noted only in younger COPD men (OR = 5.71, 95%CI 1.94–16.82).

Discussion

The potential effects of COPD on the cardiovascular system may have large clinical relevance because data from large longitudinal studies indicate that the leading cause of hospitalization and mortality in established COPD patients is of cardiovascular nature. [15] Thus COPD can no longer be considered a disease only of the lungs, as it is often associated with a wide variety of systemic consequences.

Several investigators suggest the potential role of systemic inflammation, a common feature in patients with COPD even in mild-to moderate stages, in order to explain the increased incidence of cardiovascular morbidity [16]. Both systemic inflammation and endothelial dysfunction are key mechanisms for atherosclerosis, and given that systemic inflammation is present in patients suffering from conditions, it can explain an excess risk of cardiovascular morbidity and mortality [10]. The systemic inflammation induced by smoking may also cause chronic heart failure, metabolic syndrome and other chronic diseases, which may contribute to the clinical manifestations and natural history of COPD.

A recent retrospective cohort study in longitudinal health care databases of Saskatchewan, Canada assessed the period prevalence of cardiovascular events and incidence of hospitalizations and mortality from cardiovascular outcomes in COPD patients [17]. The CVD rates have been shown to be increased in patients with COPD. The reported increased risks (odds ratios) of the following conditions when patients with COPD (n 511,493) were compared with matched population controls: arrhythmia 1.76, angina 1.61, acute myocardial infarction 1.61, congestive heart failure 3.84, and stroke 1.11.

Our results corroborate the results obtained in previous studies, COPD was found to be an extremely significant risk factor (p < 0.0001) in both sexes for cardiovascular events: ischemic heart disease 3.06, atrial fibrillation 2.70 and heart failure 4.49 with a higher impact in people over 60 (as shown in tables II and III). It is common knowledge that the studied CVDs are much more frequent after the age of 60 that is why we have analysed if COPD remains a risk factor in younger patients. COPD has represented an extremely significant risk factor compared to the non-COPD population of the same age. The overall risk for ischemic heart disease (OR = 4.92) and heart failure (OR = 5.14) remained increased for younger COPD patients, but atrial fibrillation did not. As for gender differences, ischemic heart disease was found to be increased in younger male COPD patients (OR = 5.93) but not in women, but

Table II. Number of cases with comorbidities in patients with and without COPD, odds ratio, 95% confidence interval and P value calculated for total (T), as well as male (M) and female (F) subgroups

		COPD (%)		nonCOPD (%)		OR	95% (CI)	P value
		Over 60 years	Under 60 years	Over 60 years	Under 60 years			
Ischemic heart disease	Total	255 (86.14%)	41 (13.86%)	2119 (71.97%)	825 (28.03%)	4.92	3.17–7.63	<0.0001
	Women	64 (94.11%)	4 (5.88%)	1208 (72.42%)	460 (27.57%)	2.57	0.75–8.83	0.24
	Men	191 (83.77%)	37 (12.84%)	911 (71.39%)	365 (28.6%)	5.93	3.63–9.57	<0.0001
Atrial fibrillation	Total	89 (97.80%)	2 (2.19%)	613 (87.94%)	84 (12.05%)	1.50	0.36–6.23	0.89
	Women	24 (100%)	0	336 (90.32%)	36 (9.67%)	2.73	0.15–47.12	0.67
	Men	65 (97.01%)	2 (2.98%)	277 (74.46%)	48 (25.54%)	1.50	0.35–6.32	0.90
Heart failure	Total	233 (91.37%)	23 (8.63%)	1382 (80.30%)	339 (19.70%)	5.14	3.14–8.42	<0.0001
	Women	53 (92.98%)	5 (7.02%)	832 (83.36%)	166 (16.64%)	7.11	2.40–21.06	0.0003
	Men	180 (90.9%)	18 (9.10%)	550 (76.07%)	173 (23.93%)	4.75	2.72–8.32	<0.0001
Diabetes mellitus type 2	Total	63 (84.00%)	12 (16.00%)	617 (72.93%)	229 (27.07%)	3.53	1.88–6.62	0.0001
	Women	13 (86.66%)	2 (13.34%)	349 (78.78%)	94 (21.22%)	4.71	1.03–21.57	0.14
	Men	50 (83.33%)	10 (16.67%)	268 (66.50%)	135 (33.50%)	2.96	1.48–5.93	0.0031
Osteoporosis	Total	19 (95.00%)	1 (5.00%)	240 (87.91%)	33 (12.09%)	1.88	0.25–13.97	0.52
	Women	18 (100%)	0	238 (88.14%)	32 (11.86%)	2.84	0.16–48.97	0.68
	Men	1 (50.00%)	1 (50.00%)	2 (66.66%)	1 (33.33%)	37.80	2.33–611.39	0.04
Lung cancer	Total	6 (85.71%)	1 (14.29%)	26 (92.85%)	2 (7.15%)	31.33	2.81–349.37	0.03
	Women	0	0	13 (100%)	0	–	–	–
	Men	6 (85.71%)	1 (14.29%)	13 (86.66%)	2 (13.34%)	18.89	1.69–211.12	0.12
Depression	Total	9 (69.23%)	4 (30.77%)	209 (56.33%)	162 (43.67%)	1.53	0.55–4.25	0.60
	Women	4 (100%)	0	153 (53.12%)	135 (46.88%)	0.65	0.03–11.08	0.81
	Men	5 (55.55%)	4 (44.45%)	56 (67.46%)	27 (32.54%)	5.71	1.94–16.82	0.002

heart failure correlated significantly with COPD in younger women as well (OR = 7.11). This data shows that even excluding age as a concomitant risk factor, COPD represents a risk factor not only globally but also in subgroups represented by the gender distribution and age categories.

In COPD, these comorbid conditions are regular features of general practice, some being an indirect consequence of COPD and arising independently but more likely to occur when COPD is present (i.e., ischemic heart disease, lung carcinoma, and osteoporosis) [18]. Other comorbidities may coexist with COPD because they become prevalent as part of the aging process, such as diabetes mellitus.

There is some evidence that COPD and metabolic syndrome may be related, perhaps through systemic inflammation, which is common to both [4]. This was further supported by the finding that metabolic syndrome was more common among people with advanced COPD, compared with age- and sex-matched controls [19]. However, an association between airflow obstruction, a hallmark of COPD, and metabolic syndrome was not observed in three recent cross-sectional studies, two in population samples from Taiwan and Japan [5], and one in healthy attendees of a day care centre and a home for the aged in Italy [20].

In our case, association with type 2 diabetes was extremely significant in COPD men, including those under 60. But, apparently the impact of COPD on diabetes was not increased by the presence of COPD in women, even over the age of 60. This controversial result limits the understanding of the joint aetiology of COPD and metabolic syndrome.

Significant correlation with osteoporosis was found in women, all of them over 60 years (OR = 3.19) and in the subgroup of men under 60 (OR = 37.80). This could be explained by the fact that osteoporosis is under-diagnosed and it is not actively searched in COPD patients, as being the case for depressive conditions as well. In comparison to other studies the overall impact of COPD on depressive disorders was not observed in our study, it was mainly diagnosed in younger COPD men (OR = 5.71). Depression, anxiety and osteoporosis are also common in elderly COPD patients; these factors severely affect their quality of life [12]. However, older patients perceive their symptoms differently, and COPD could also be under-diagnosed in this population. The management of elderly patients with COPD should encompass a multidisciplinary approach. An evaluation of patients' nutritional status and mental health should be undertaken, in addition to assessing their heart and lung function and functional impairment. Significant underlying co-morbidities should be evaluated and treated to derive the maximal benefit of therapy [7].

Other pathologies linked to COPD were investigated as well. There is recent evidence that chronic inflammation may play a significant role in the pathogenesis of lung cancer as a tumor promoter. This is supported by several reports showing that chronic inflammation has a relevant role in triggering cancer [21]. Lung cancer was diagnosed only in COPD men compared to women; the association of COPD represents a very significant additional risk compared to patients without COPD. Interestingly, women with lung cancer were not associated with COPD, and age appears to influence risk of developing cancer as the majority of the patients were over 60 years old.

The management of comorbidities is difficult in the presence of COPD because all of them amplify the disabil-

ity associated with COPD and can potentially complicate its management. Comorbid conditions in patients with COPD are very common; at least one comorbidity can be present in 84% of patients, and can influence the observed pattern of deterioration of health-related quality of life with worsening of disease [22]. However, medical textbooks and evidence-based clinical guidelines still largely ignore the fact that COPD seldom occurs in isolation [7].

Our results seem to indicate that COPD is a risk factor for these comorbid conditions, although we cannot exclude the possibility of a concomitant disease that has appeared to a certain extent by sharing the same risk factor (smoking) or by chance.

All in all, COPD is a common, costly, and preventable disease that has substantial implications for the health of human beings. Lung cancer and CVD are common causes of death in the natural course of COPD, being influenced by the severity of airflow limitation. The potential introduction of the new term "chronic systemic inflammatory syndrome" points to the relevance of common risk factors in the development not only of COPD, chronic heart failure, or metabolic syndrome, but also of complex systemic disturbances affecting other organs, all possibly reflecting the vital role played by systemic inflammation.

Conclusions

1. These findings support the conclusion that COPD is an independent risk factor for CVD. Knowing that COPD is an independent risk factor for CVD has many repercussions. A concerted effort to evaluate a patient with symptomatic yet undiagnosed COPD may be essential to determine a patient's cardiovascular status. Another indication would be to use a preventive medicine approach with a COPD patient making lifestyle choices clearly protective of CVD in their future. Lastly, further investigation of systemic inflammation as a culprit in the cascade of ensuing pathology as an underlying primary factor in both COPD and CVD is warranted.
2. The search for the most frequent comorbidities of COPD may be instrumental and of great help to improve our understanding of the complexities of the interplay between COPD, and comorbidities, like diabetes, osteoporosis, lung cancer and depression. This will ultimately improve our combat against COPD and its spectrum of major risk factors.
3. The present findings provide evidence suggesting that future guidelines should evolve and develop a holistic approach to the treatment of chronic diseases in order to meet the challenge of an ageing society.

Acknowledgment

This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU 80641.

References

1. Agusti A, Soriano JB. COPD as a systemic disease. Copd. 2008;5(2):133-8.
2. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD Executive Summary. Am J Respir Crit Care Med 2007;176:532–555
3. Agusti AGN, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003;21:347–360.
4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415–1428.
5. Lam B.H., Jordan R.E., C.Q. Jiang, G.N. Thomas, M.R. Miller, W.S. Zhang, Lam T.H., Cheng K.K., Adab P.: Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study K- Eur Respir J 2010; 35: 317–323)
6. Fabbri LM, Luppi F, Beghe´ B, et al. Complex chronic comorbidities of COPD. Eur Respir J 2008; 31: 204–212.
7. Barnes P.J., Celli B.R.Systemic manifestations and comorbidities of COPD Eur Respir J 2009; 33: 1165–1185
8. Schneider C, Bothner U, Jick S.S., et al. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases European Journal of Epidemiology 2010; aop: 10.1007/s10654-010-9435-7
9. MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005; 2: 50–60.
10. Sin DD, Man SF. Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease. Can J Physiol Pharmacol. 2005;83(1):8-13.
11. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace. 2006;8(9):651-745.
12. Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, Plaza V, Prieto L, Anto´ JM. Chronic obstructive pulmonary disease stage and health-related quality of life. The Quality of Life of Chronic Obstructive Pulmonary Disease Study Group. Ann Intern Med 1997;127: 1072–1079.
13. Rodriguez-Roisin R, Soriano JB. Chronic obstructive pulmonary disease with lung cancer and/or cardiovascular disease. Proceedings of the American Thoracic Society. 2008;5(8):842-7.
14. Kikeli P., Kikeli Sz., Gál B., Stanciu L. et al - Medprax – Database for an integrated Health Care System A XII-a Sesiune Stiintifica a Muzeului Ardelean, Târgu Mures, 2002, Vol. Rezumate P.15
15. Lopez A.D., K. Shibuya, C. Rao, C.D. Mathers, A.L. Hansell, L.S. Held, V. Schmid and S. Buist Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006; 27: 397–412
16. Johnston AK, Mannino DM, Hagan GW, Davis KJ, Kiri VA. Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. Thorax. 2008;63(7):599-605.
17. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol. 2006;16(1):63-70.
18. Sevenoaks MJ, Stockley RA. Chronic Obstructive Pulmonary Disease, inflammation and co-morbidity–a common inflammatory phenotype? Respir Res 2006;7:70.
19. Fimognari FL, Pasqualetti P, Moro L, et al. The association between metabolic syndrome and restrictive ventilatory dysfunction in older persons. J Gerontol A Biol Sci Med Sci 2007; 62: 760–765.
20. Cazzola M, Bettoncelli G, Sessa E, Cricelli C, Biscione G.: Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. Respiration. 2010 Feb 4. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/20134148?dopt = Abstract
21. Lee G, Walser TC, Dubinett SM Chronic inflammation, chronic obstructive pulmonary disease, and lung cancer. Current opinion in pulmonary medicine, 2009, 15/4(303-7), 1531-6971
22. Curkendall SM, Lanes S, de Luise C, Stang MR, Jones JK, She D, et al. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. Eur J Epidemiol. 2006;21(11):803-13.