METABOLIC SYNDROME (METS) AS ONE OF THE MAJOR COMORBIDITIES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Aim: *We aimed to investigate the association between COPD and MetS, the relation to the severity of airflow limitation.*

Methods: *This is a cross-sectional study including 220 patients with initially diagnosed COPD (IG), aged 40 to 75 years and 58 non-COPD subjects matched by age, smoking status, body mass index, as controls (CG). All study participants underwent anthropometric measurements, fasting blood sugar (FBS), lipid profile, pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses, chest X-ray).*

Results: *Results presented statistically significant difference in presence of MetS in COPD patients compared to controls (32.27% vs 10.34%; P=0.0009). According to the GOLD classification, the frequencies of MetS in COPD patients were categorized in stages I, II, III, IV (17.54%, 37.10%, 34.62%, 40.82%, respectively). The proportion of patients with increased glycemic values was: a) GOLD1 - 18 (31.58%); b) GOLD 2 - 32 (51.61%); c) GOLD3 - 29 (55.77%); and d) GOLD4 - 31 (63.27%). There was no significant difference between IG and CG patients regarding HDL level. According to arterial hypertension the highest proportion was observed in GOLD3 - 22 (42.31%) followed by GOLD4 - 20 (40.82%), and GOLD3 - 22 (35.48 %), smallest in GOLD1 - 17 (29.82%).*

Conclusion: *We found higher prevalence of MetS in patients with COPD even in early COPD stages compared to non-COPD. Our findings suggest an urgent need to develop comprehensive strategies for prevention, screening and start of treatment in early stage.*

Key words: *COPD, metabolic syndrome, dyslipidemia, obesity.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that causes obstructed airflow limitation from the lungs. COPD is currently the third leading cause of death worldwide presented by persistent, chronic inflammation of the airway, damage of the alveoli, and bronchoconstriction [1]. The underlying cause of COPD is the inflammatory response to inhaled particles (cigarette smoke, air pollution) which have a wide range of destructive consequences [2]. Airway inflammatory process is responsible for influx of inflammatory factors into the vessels and spreading in different tissues and organs which leads to extrapulmonary manifestations like cardiovascular comorbidity, musculoskeletal damage, osteoporosis, psychological manifestations, and metabolic syndrome (MetS) [3]. Cardiovascular complications are the main risk factor for hospitalization and death in patients with COPD. Hypoxia lead to pulmonary vasoconstriction, pulmonary hypertension, enlarged afterload in right ventricle, compensatory right ventricular hypertrophy and dilatation, left ventricular dysfunction, and cor pulmonale [3, 4]. On the other side tobacco smoke is a risk factor for systemic inflammation which leads to atherosclerosis, thrombosis and organ aging [3]. The most important metabolic comorbidities of COPD are: MetS and diabetes mellitus type 2 (T2DM) [1]. The MetS is found to be more frequent in COPD. Many inflammatory mediators are detected in COPD patients in sputum, blood, broncho-alveolar specimen indicating the presence of persistent, low-grade systemic inflammation as a major risk factor for both COPD and MetS [5]. MetS is a complexity of abdominal obesity, arterial hypertension, hyperglycemia, and hyperlipidemia [elevated triglycerides (TRG) and low levels of high-density lipoprotein (HDL) and/or elevated cholesterol (CHOL)]. MetS may induce atherosclerosis, also increases the possibility to develop type 2 diabetes [6]. There are many published data suggesting that MetS is more frequent in COPD than in population

without respiratory disease. These diseases share similar underlying mechanisms of cigarette smoking, obesity (especially neck obesity), corticosteroid usage (promotor of central obesity, retention of fluids), physical inactivity, hypoxia and oxidative stress [7]. These comorbidities, especially CVD, T2DM, and MetS, are associated not only with a higher risk of hospitalization and mortality but also with the increased economic burden of COPD. The management of patients with COPD must include the identification and treatment of its comorbidities, as these have a significant impact on COPD prognosis [4]. World Health Organization (WHO) in 1998, poposed the definition MetS instead of previous Syndroma X, Reaven Sy, insulin resistence etc. The MetS prevalence has epidemic prevalence, 20-25% of population in United States and Australia has been diagnosed with MetS [8]. The incidence of MetS often parallels the incidence of obesity and incidence of T2DM (one of the outcome of MetS). According to NHANES data, during 1988–2010, average BMI in USA increased by 0.37% per year in both men and women and waist circumference (WC) increased by 0.37 and 0.27% per year in women, respectively [9]. The aim of this study was to access the prevalence of MetS in COPD patients and the relation to the severity of airflow limitation.

MATERIAL AND METHODS

Study design and setting

Frequency of MetS in newly diagnosed patients with COPD and non-COPD controls was conducted in the period 2018-2020 as a cross-sectional analysis.

Study approval

The study was approved by the Ethics Committee of the Medical Faculty, protocol number 03-2237/5/21.05.2018.

Informed consent

Written informed consent was obtained from all participants.

Study subjects

Study subjects represented 278 participants separated in Investigated Group (IG) composed of 220 (79.1%) patients with initial diagnosis of COPD and 58 (20.9%) controls where COPD was excluded (CG). Controls were matched to IG by gender, body mass index (BMI), age and smoking history. Before entering the study all subjects signed informed consent.

Inclusion criteria for IG: age 40-75 years old, initial diagnosis of COPD based on GOLD (Global Initiative for Chronic Obstructive Lung Disease), active or ex-smokers (>10 pack-years), signed informed consent. Exclusion criteria for IG: age < 40 years and >75 years, other chronic pulmonary diseases (bronchiectasis, asthma, active tuberculosis, pulmonary fibrosis, sarcoidosis, lung cancer), chronic diseases in liver, kidneys, anemia, patients that refused participation, spirometry contraindications. Inclusion criteria for CG: age 40-75 years, active or ex-smokers (>10 pack-years), clinically stable, with normal functional pulmonary tests, without diagnosed lung diseases, who agreed to participate.

Study protocol

In this included cross-sectional analysis was included lung and metabolic evaluation. According to World Health Organization (WHO) criteria, smoking history of the subjects was implemented for classification as current and former smokers [10]. European Community for Coal and Steel questionnaire (ECCS - 87) and European Community Respiratory Health Survey (ECRHS) questionnaire was included to analyze subject's symptoms during the last year (cough, chest tightness, wheezing, dyspnea, phlegm) [11, 12].

Respiratory analysis

The pulmonary evaluation was composed of spirometry (pre- and post-bronchodilator), dyspnea severity, gas analysis, chest radiography.

British Medical Council Dyspnea Scale was used for dyspnea severity assessment [15]. Baseline spirometry (pre-bronchodilator) analyzed forced expiratory volume in 1st second (FEV1), forced vital capacity (FVC), FEV1/FVC, maximal expiratory flow at 75%, 50%, 25%, and 25-75% of FVC (MEF75, MEF50, MEF25, and MEF25-75), according to European Respiratory Society (ERS) and ATS (American Thoracic Society).

Irreversible bronchoconstriction was defined if post-bronchodilator FEV1/FVC index stayed < 70%. The degree of FEV1 reversibility was expressed as % FEV1 reversibility ([post-bronchodilator FEV1 – pre-bronchodilator FEV1] / pre-bronchodilator FEV1 x 100) [13]. Presence of fixed bronchoconstriction, post-bronchodilator FEV1/FVC< 70%, in the participants with anamnesis of chronic cough or a production of sputum, dyspnea, risk factors exposition (smoke from home cooking, cigarette smoke, heating fuels, occupational chemicals and dust) were criteria for diagnosis of COPD. According the degree of bronchoconstriction, COPD subjects were divided in GOLD 1 (mild), GOLD 2 (moderate), GOLD 3 (severe), and GOLD 4 (very severe) [1, 13, 14]. GOLD 1 (FEV_1 > 80% of the predicted value), GOLD 2 (FEV_1 > 50% but < 80% of the predicted value), GOLD 3(FEV_1 > 30% but < 50% of the predicted value), and GOLD 4 (FEV_1 < 30% of the predicted value) [1].

Metabolic evaluation

According to American Heart Association (AHA), MetS is defined by the presence of five criteria:

1. Presence of T2DM, or glucose > 6.5 mmol/L, or 2 h glucose > 7.8 mmol/L;
2. HDL < 1.03 mmol/L in men, < 1.3 mmol/L in women;
3. TRG > 1.7 mmol/L;
4. Waist circumference > 102cm (men) or > 88cm (women) or BMI > 30 kg/$m^{2;}$
5. Arterial blood pressure > 130/85 mmHg [15].

Biochemical tests, i.e. determination of serum CHOL, HDL and LDL (low density lipoprotein) values, serum TRG and glycaemia were performed on the ARCHITECT c4000 device (Abbott, Abbott Park, Illinois, USA). Reference values of serum CHOL 4.2 - 5.2 mmol/L, HDL 1.0 - 2.0 mmol / L, LDL 2.2 - 3.7 mmol / L, TRG 0.30 -1 .70 mmol / L and for glycaemia 4.1 - 5.9 mmol / L. Subjects with serum CHOL values > 5.2 mmol / L and/or serum TRG values > 7 mmol / L, as well as those with data from the medical documentation on diagnosed hyperlipidemia and use of hypolipemic agents (statins or fibrates) are considered subjects with dyslipidemia.

Statistical analysis

1. Statistical analysis was done with using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows. Analyses of the data included testing the differences in prevalence, comparison of the means, and testing the association mentioned above. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages, so the comparison between them was performed with the Pearson Correlation Test. The significance level (*P*-value) of less than 0.05 was considered as statistically significant [4, 11].

RESULTS

Analysis of the parameters of interest in IG and CG presented similarities according to sex, smoking status, mena BMI, age. The mean age of IG subjects was 65.1±6.8 [95% CI (64.2–65.9)] years with a min/max age of 45/78 years. The analysis indicated that 50% of respondents in the IG were older than 65 years for Median (IQR)=65 (59-70). Among CG subjects, the mean age was 58.55±13.44 [95% CI (58.6 – 62.7)] years, with a min/max age of 45/76, and 50% of subjects older than 59 years for Median (IQR)=59 (56-67).

The mean values of spirometry parameters (FVC, FEV_1, FEV_1/FVC) were significantly lower in IG than in CG (Table 1).

BMI – to assess nutrition was used, which was calculated as body weight (kg) / body height (m2). The analysis indicated an irregular distribution of frequencies for the obtained values of BMI (kg/m²) for Shapiro-Wilk W=0.9746; p=0.00007, which is why appropriate non-parametric statistical tests were used for the analyses. For p>0.05, no significant difference was determined between the four subgroups of IG in terms of BMI level (Kruskal- H test: Chi-square (3) = 1.735; p = 0.6291) (Table 2, Figure 1).

According to the international reference values for BMI, the subjects were divided into three nutrition groups, namely: a) normal nutrition; b) overweight; and c) obesity (Table 3). International cut-off values defined for normal (<25 kg/m2), overweight (25-

29.9 kg/m2) and obese (>30 kg/m2) were used to group the quantitative values of BMI. According to Table 3, the distribution according to nutrition (normal, overweight, obese) was consistent for: a) GOLD1 – 24 (42.1%) vs. 29 (50.9%) vs. 4 (7%); b) GOLD2 – 26 (41.9%) vs. 30 (48.4%) vs. 6 (9.7%); c) GOLD3 – 26 (50%) vs. 19 (36.5%) vs. 52 (23.6%); d) GOLD4 – 26 (53.1%) vs. 17 (34.7%) vs. 6 (12.2%); e) IG - 102 (46.4%) vs. 95 (43.2%) vs. 23 (10.4%); and f) CG-15 (25.9%) vs. 37 (63.8%) vs. 6 (10.3%). For $p>0.05$, the analysis did not indicate a significant association between the nutrition of the subjects and the subgroup (GOLD 1 → GOLD 4) to which they belonged (Fisher Freeman Halton test: p=0.5558). The analysis between the two groups of IG/CG indicated that, for $p<0.05$, there is a significant association between nutrition and the group to which the subjects belong (Pearson Chi-square test: X2=8.691; df=2; p=0.0129). CG subjects were 2.648 times more likely to be overweight than normally fed compared to IG [OR=2.65 (1.37–5.13) 95% CI]. For $p>0.05$, there was no significant association between the group where the subjects belonged and obese/normal BMI status.

For $p<0.05$, the analysis indicated a significant difference between the four subgroups of IG regarding the serum **TRG level** (Kruskal-Wallis test: H(3)=12.842; p=0.005 (Table 4). This significance was due to the significantly lower level of TRG in GOLD4 compared to: a) GOLD1 (Mann-Whitney U Test: Z=3.213; p=0.001).

The proportion of patients with increased **glycemic values** was in: a) GOLD1 - 18 (31.58%); b) GOLD 2 - 32 (51.61%); c) GOLD3 - 29 (55.77%); and d) GOLD4 - 31 (63.27%). For $p<0.05$, a significant association was determined between the subgroup of IG to which the subjects belonged and the glycemic status for the Pearson Chi-square test: X2=11.943; df = 3; p=0.0076. For $p>0.05$, there was no significant difference between IG and CG patients regarding **HDL level** (Mann-Whitney U Test: Z=1.127; p=0.068).

Subgroups and groups of subjects were also analyzed according to the presence of **arterial hypertension**, where the highest proportion was observed in GOLD3 - 22 (42.31%) followed by GOLD4 - 20 (40.82%), and GOLD3 - 22 (35.48 %), as well as the smallest in GOLD1 - 17 (29.82%). The proportional representation of subjects with arterial hypertension in IG or CG was consistently 81 (36.82%) vs. 16 (27.59%). For $p>0.05$, there was no significant association between the group to which the subjects belonged (IG/CG) and the presence of arterial hypertension (Pearson Chi-square test: X2=1.722; df=1; p=0.1894) (Figure 2).

The proportion of subjects with **metabolic syndrome** was the highest in GOLD4 - 20 (40.82%) followed by GOLD2 - 23 (37.10%), GOLD3 - 18 (34.62%) and the lowest in GOLD1 - 10 (17.54%). For $p<0.05$, a significant association was established between the subgroup of IG to which the subjects belonged and the finding of MetS by Pearson Chi-square test: X2=8.084; df = 1; p=0.0443. Additional analysis indicated that, for $p<0.05$, this significance was due to a significantly greater association of a finding of MetS with belonging to the GOLD1 subgroup compared to GOLD2, GOLD3 and GOLD4 for a consequent Pearson Chi-square test: X2=5.665; df = 1; p=0.0173 vs. X2=4.151; df = 1; p=0.0416 vs. X2=7.033; df = 1; p=0.008. In GOLD2, the finding of MetS was 2.77 times more common than in GOLD1. The proportional representation of a finding of MetS in IG or CG was consistently 71 (32.27%) vs. 6 (10.34%) For $p<0.05$, a significant association of MetS findings with IG subjects was determined (Pearson Chi-square test: X2=11.021; df=1; p=0.0009). Subjects from IG had 4.129 times more often a positive finding for MetS compared to those from CG [OR=4.129 (1.69–10.07) 95% CI] (Table 5, Figure 3).

An analysis of the relationship between COPD and MetS was performed. The association was tested in relation to the four stages of COPD (GOLD1→GOLD4 in IG) as well as in relation to the presence/absence of COPD (IG/CG) (Figure 4). The analysis with Spearman Rank order correlations indicated that between metabolic syndrome and GOLD stages of COPD, for $p<0.05$, there was a significant linear positive weak correlation R(220)=0.161; p=0.0167. As FEV1 decreased (GOLD1→GOLD4), the frequency of MetS increased significantly. For $p<0.05$, a significant positive weak correlation was determined between the finding of MetS and the presence of COPD (CG→IG) for R(278)=0.199; p=0.0001. In IG there was a significant increase in positive findings for metabolic syndrome. The potential predictive role of COPD for a positive finding of metabolic syndrome

was analyzed for the entire sample, and individually in terms of gender (men/women), smoking status (former/current) and nutrition (normally fed - BMI<25 kg/m2 / over-fed - BMI≥25 kg/m2). Adjustment was made taking into account potential confounding factors such as: gender – men vs. women; age; occupational exposure – yes vs. no; Brinkman index; CHOL (mmol/l); TRG (mmol/L); HDL (mmol/L); and BMI (kg/m²). For $p<0.05$, the finding of metabolic syndrome was significantly negatively associated with COPD in men before adjustment for p=0.046 [OR=0.487 (0.24-0.99) 95% CI] and in ex-smokers before adjustment for p=0.022 [OR=0.328 (0.13-0.85) 95% CI]. For $p>0.05$, after adjustment, no significant association of COPD with any of the analyzed aspects was observed (Figure 5).

DISCUSSION

The relationship between the metabolic syndrome and COPD has been investigated in several longitudinal and cross-sectional studies, and the obtained results indicate that the metabolic syndrome is an independent risk factor for the worsening of respiratory symptoms and lung function, as well as for the occurrence and progression of PAH [16]. In our study the prevalence of arterial hypertension was higher in COPD subjects (36.82%) than in non-COPD controls (27.59%) but the difference was not statistically significant. In regard to certain subgroups, the prevalence of hypertension was higher in the subgroups GOLD 3 and GOLD 4 than in the subgroups GOLD 1 and GOLD 2 but the difference was also non-significant. The prevalence of metabolic syndrome was more in IG (statistically significant) than in CG (32.27 vs. 10.34; p = 0.0009), and its frequency within subgroups of IG increases with decreasing of the FEV1 value (GOLD 1→GOLD 4). The obtained results are complementary to the results of several studies published in the last five years. One of them is the 2016 meta-analysis. which analyzed 19 studies involving 4208 subjects with COPD, which indicates a frequency of metabolic syndrome of 34%. In subjects with COPD and metabolic syndrome in this study, a higher frequency of female sex, higher values of body mass index and lower values of FEV1 were recorded compared to subjects with COPD who did not have metabolic syndrome [17]. In a retrospective analysis by Choi from 2019 where 2164 patients with chronic obstructive pulmonary disease in its initial stages (GOLD1 and 2) were included, a frequency of metabolic syndrome of 31.2% was registered, and it was significantly associated with female gender, advanced age and the presence of cardiovascular comorbidities [18]. The results of research conducted in India indicate a frequency of metabolic syndrome of 27 to 44% [8, 19, 20]. In contrast, according to the results of research conducted in Japan, the comorbidities of COPD with the highest frequency are malnutrition and osteoporosis. The frequency of the metabolic syndrome is about 20%, which according to the authors of these studies is due to the dominant emphysematous phenotype of COPD and the lower values of the body mass index in the subjects involved. The Copenhagen City Heart Study showed that in individuals with COPD, the relative mortality risk was highest in those in the lowest BMI category (<20.0 kg/m2) [21]. In order to determine the association between BMI and the declining rate of FEV1 in COPD patients, a systematic analysis of many published, randomized clinical trials with 27,000 participants was performed and showed that the decrease in BMI was strongly associated with a faster drop in the value of FEV1[22, 23].

CONCLUSION

The frequency of the metabolic syndrome is statistically significantly higher among subjects from IG compared to CG. Its frequency within the subgroups of IG increases with the decrease in FEV1 value (GOLD1→ GOLD4) which is due to the statistically significantly higher frequency of metabolic syndrome in subjects from subgroups GOLD2, GOLD3 and GOLD4 compared to subgroup GOLD1. These findings signify that the screening of metabolic syndrome is necessary and stratification for cardiovascular disease risk is important for timely intervention to prevent and decrease the morbidities and mortalities.

MAIN POINTS

1. The frequency of dyslipidemia (increased values of serum triglycerides, cholesterol or triglycerides and cholesterol) was higher in IG for all three parameters compared to CG.
2. According to IG subgroups, the frequency of subjects who did not have dyslipidemia was highest in the GOLD1 subgroup, and lowest in the GOLD4 subgroup (GOLD1→ GOLD4).
3. The frequency of arterial hypertension was higher in IG subjects (36.82%) compared to its frequency in CG subjects (27.59%). In terms of the frequency of hypertension in IG subgroups, the highest frequency was registered in the GOLD3 subgroup, followed by GOLD4, GOLD2 and GOLD1 subgroups.
4. The frequency of metabolic syndrome was statistically significantly higher in IG subjects (32.72%) compared to CG (10.34%). Its frequency within IG subgroups increased as the value of FEV1 (GOLD1→ GOLD4) decreased.
5. We found higher prevalence of MetS in patients with COPD even in early COPD stages compared to non-COPD. Our findings suggest an urgent need to develop comprehensive strategies for prevention, screening and start of treatment in early stage. Metabolic syndrome is an independent risk factor for the worsening of respiratory symptoms and lung function in COPD patients, worse quality of life and prognosis.

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Rezime: Metabolički sindrom (MetS) kao jedna od glavnih komorbidnosti hronične opstruktivne plućne bolesti (COPD)

Cilj: *Imali smo za cilj da istražimo asocijaciju između COPD-a i MetS-a, odnos prema ozbiljnosti ograničenja protoka vazduha.*

Metod: *Ovo je presek studije koja uključuje 220 pacijenata sa prvobitno dijagnostikovanim COPD (IG), starosti od 40 do 75 godina i 58 ne-COPD subjekata koji se podudaraju sa godinama, statusom pušenja, indeksom telesne mase, kao kontrolama (CG). Svi učesnici studije podvrgnuti su antropometrijskim merenjima, postu šećera u krvi (FBS), lipidnom profilu, plućnoj proceni (procena ozbiljnosti disspneje, osnovna linija i post-bronhodilatorska spirometrija, analiza gasova, rendgen grudnog koša).*

Rezultati: *Rezultati su pokazali statistički značajnu razliku u prisustvu MetS-a kod pacijenata COPD-a u poređenju sa kontrolama (32,27% naspram 10,34%; P=0.0009). Prema GOLD klasifikaciji, frekvencije MetS-a kod pacijenata COPD-a kategorisane su u fazama I, II, III, IV (17,54 odsto, 37,10 odsto, 34,62 odsto, 40,82 odsto). Proporcija pacijenata sa povećanim glicemičkim vrednostima bila je: a) GOLD1 - 18 (31,58%); b) ZLATO 2 - 32 (51,61%); c) GOLD3 - 29 (55,77%); i d) GOLD4 - 31 (63,27%). Nije bilo značajne razlike između IG i CG pacijenata u pogledu nivoa HDL-a. Prema arterijska hipertenziji najveća proporcija zabeležena je u GOLD3 - 22 (42,31 odsto), a slede GOLD4 - 20 (40,82 odsto), a GOLD3 - 22 (35,48 odsto), najmanji u GOLD1 - 17 (29,82 odsto).*

Zaključak: *Pronašli smo veću rasprostranjenost MetS-a kod pacijenata sa COPD-om čak i u ranim COPD fazama u poređenju sa ne-COPD- om. Naši nalazi sugerišu hitnu potrebu da se razviju sveobuhvatne strategije prevencije, skrininga i početka lečenja u ranoj fazi.*

Ključne reči: *HOBP, metabolički sindrom, dislipidemija, gojaznost.*

KEY WORDS: *Covid 19, anxiety, depression,*

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ADDITIONAL FILES

Table 1. Distribution of the COPD patients by degree of airflow limitation and gender

Groups/ Subgroups	Gender			[1]p
	Male	Female	Total	
GOLD 1	43 (75.44%)	14 (25.56%)	57 (2.91%)	X^2=0.358; df=3; p=0.9488
GOLD 2	47 (75.81%)	15 (24.19%)	62 (18.18%)	
GOLD 3	38 (73.01%)	14 (29.92%)	52 (23.64%)	
GOLD 4	35 (71.43%)	14 (28.57%)	49 (22.27%)	
IG	163 (74.09%)	57 (25.91%)	220 (79.14%)	X^2=0.272; df=1; p=0.6021
CG	41 (70.69%)	17 (29.31%)	58 (20.86%)	
IG = Investigated Group; CG = Control Group; [1]Pearson Chi-square test; *significance p < 0.05				

Table 2. Analysis of groups/subgroups according to airflow limitation and Body Mass Index (BMI)

BMI	Number (N)	Mean	Standard deviation (SD)	Minimum (Min)	Maximum (Max)	Median IQR	p
IG – subgroups							
GOLD 1	57	25.41	3.59	19.9	35.5	25.7 (23.2-27.2)	Kruskal-Wallis H test: Chi-square (3)=1.735; p=0.6291
GOLD 2	62	25.85	3.28	19.8	34.9	25.5 (23.4-27.8)	
GOLD 3	52	25.27	4.19	17.6	34.4	24.9 (22.2-27.5)	
GOLD 4	49	25.12	4.10	18.6	34.6	24.7 (22.1-27.3)	
Groups							
IG	220	25.44	3.76	17.6	35.5	25.3 (22.9-27.4)	Mann-Whitney U Test:: Z=-1.896; p=0.058
CG	58	26.22	2.50	19.4	33.2	26.2 (24.6-27.1)	
Investigated Group = IG; Control group = CG; *significant for p < 0.05							

Figure 1. Analysis of groups/subgroups according to Body Mass Index (BMI)

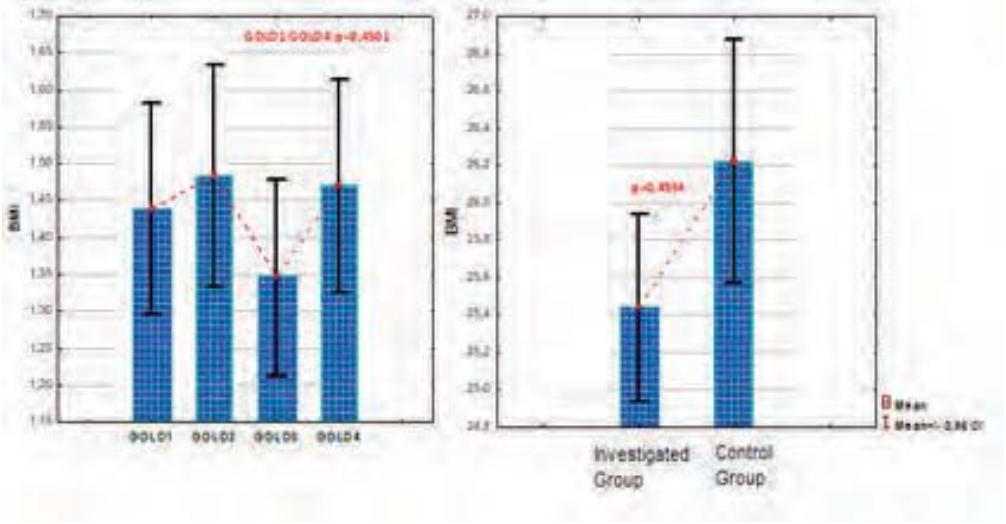

Table 3. Analysis of groups/subgroups according to Body Mass Index (BMI)

Subgroups/ Groups	Body Mass Index (BMI groups)				[1]p
	Normal	Overweight	Obese	Total	
IG - subgroups					
GOLD 1	24 (42.11%)	29 (50.88%)	4 (7.02%)	57 (25.91%)	Fisher Freeman Halton test: p=0.5558
GOLD 2	26 (41.94%)	30 (48.39%)	6 (9.68%)	62 (18.18%)	
GOLD 3	26 (50%)	19 (36.54%)	7 (13.46%)	52 (23.64%)	
GOLD 4	26 (53.06%)	17 (34.69%)	6 (12.24%)	49 (22.27%)	
Groups					
IG	102 (46.36%)	95 (43.18%)	23 (10.45%)	220 (79.14%)	Pearson Chi-square test: X^2=8.691; df=2; p=0.0129*
CG	15 (25.86%)	37 (63.79%)	6 (10.34%)	58 (20.86%)	

IG=Investigated Group; CG=Control Group; overweight: 25-29,9 kg/m^2; obese: >30 kg/m^2
*significant for p<0.05

Table 4. Analysis of groups/subgroups according to glycemic and lipid profile

Parameters	Subgroups					Groups	
	GOLD 1 N=57	GOLD 2 N=62	GOLD 3 N=52	GOLD 4 N=49	p	IG N=220	CG N=58
Glycemic profile							
Normal (<6mmol/L after 12 hours fasting)	39 (68.42%)	30 (48.39%)	23 (44.23%)	18 (36.73%)	Pearson Chi-square test: X^2=11.943; df=3; p=0.0076*	110 (50%)	39 (67.24%)
Elevated (>6mmol/L after 12 hours fasting)	18 (31.58%)	32 (51.61%)	29 (55.77%)	31 (63.27%)	Pearson Chi-square test: X^2=5.486; df=1; p=0.0192*	110 (50%)	19 (32.76%)
Cholesterol – CHOL (mmol/l)							
$\overline{X}$ ± SD	4.65±1.07	4.79±1.09	4.91±1.01	4.84±1.34	Kruskal-Wallis test: H (3)=2.303; p=0.5119	4.79±1.12	4.88±1.07
Median (IQR)	4.5 (3.9-5.2)	4.7 (4.1-5.7)	4.6 (4.2-5.4)	4.7 (3.7 -6)		4.6 (4.1-5.4)	5 (4.3-5.5)
p	-					Mann-Whitney U Test:: Z=-1.187; p=0.2352	
Tryglicerids – TRG (mg/dL)							
$\overline{X}$ ± SD	1.92±0.99	1.36±0.71	1.34±0.62	1.02±0.35	Kruskal-Wallis test: H (3)=12.842; p=0.005*	1.34±0.74	1.41±0.69
Median (IQR)	1.3 (0.9-1.7)	1.2 (0.8-1.6)	1.2 (0.9-1.4)	1 (0.7 -1.2)		1.2 (0.8-1.5)	1.3 (1.1-1.6)
p	GOLD1/GOLD2: Z=0.968; p=0.339; GOLD1/GOLD3: Z=1.031; p=0.302; GOLD1/GOLD4: Z=3.213; p=0.001*; GOLD2/GOLD3: Z=-0.074; p=0.941; GOLD2/GOLD4: Z=2.601; p=0.009*; GOLD3/GOLD4: Z=2.708; p=0.007*;					Mann-Whitney U Test:: Z=-1.484; p=0.1377	
High Density Lipoprotein - HDL (mmol/L)							
$\overline{X}$ ± SD	1.29±0.46	1.24±0.39	1.26±0.35	1.27±0.30	Kruskal-Wallis test: H (3)=0.397; p=0.941	1.27±0.38	1.17±0.35
Median (IQR)	1.3 (0.8-1.8)	1.2 (0.9-1.5)	1.2 (1-1.5)	1.3 (1 -1.5)		1.3 (0.9-1.5)	1.1 (0.9-1.3)
p	-					Mann-Whitney U Test:: Z=1.827; p=0.068	

IG=Investigated Group; CG=Control Group; Z=Mann-Whitney U Test;
*significant for p<0,05

Figure 2. Distribution of subgroups/groups according to arterial hypertension

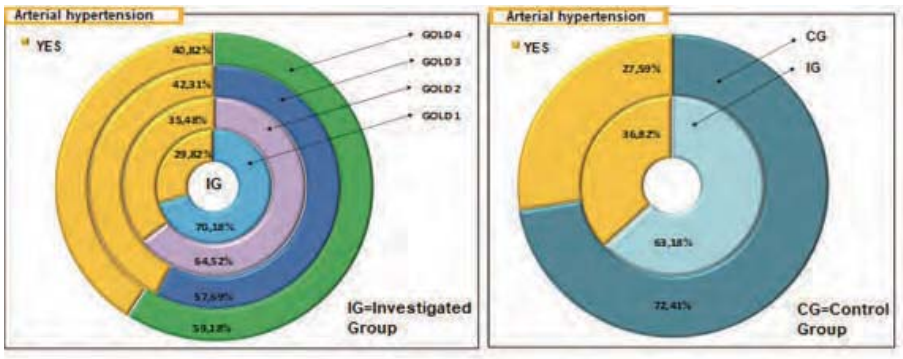

Table 5. Analysis of subgroups/groups according to positive finding for MetS

Metabolic syndrome (MetS)	Subgroups					Groups	
	GOLD 1 N=57	GOLD 2 N=62	GOLD 3 N=52	GOLD 4 N=49	p	IG N=220	CG N=58
NO	47 (8.,46%)	39 (62.90%)	34 (65.38%)	29 (59,18%)	Pearson Chi-square test: X^2=8.084; df=1; p=0.0443*	149 (67.73%)	52 (89.66%)
YES	10 (17,54%)	23 (37,10%)	18 (34,62%)	20 (40,82%)		71 (32.27%)	6 (10.34%)
p	GOLD1/GOLD2: X^2=5.665; df=1; p=0.0173*; GOLD1/GOLD3: X^2=4.151; df=1; p=0.0416*; GOLD1/GOLD4: X^2=7.033; df=1; p=0.008*; GOLD2/GOLD3: X^2=0.076; df=1; p=0.783; GOLD2/GOLD4: X^2=0.1596; df=1; p=0.6896; GOLD3/GOLD4: X^2=0.4133; df=1; p=0.5203;					Pearson Chi-square test: X^2=11.021; df=1; p=0.0009*	
IG=Investigated Group; CG=Control Group; X^2 = Pearson Chi-square test *significant for p<0,05							

Figure 3. Distribution of metabolic syndrome according to groups/subgroups

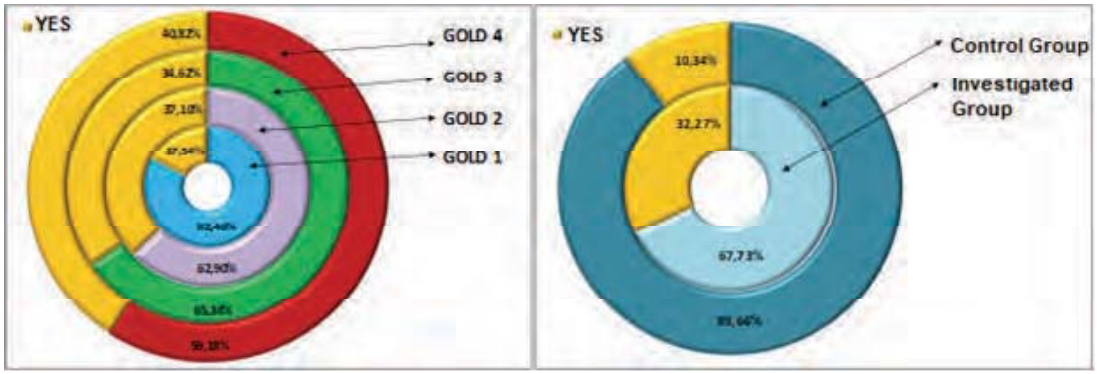

Figure 4. Correlation between COPD and metabolic syndrome according to groups/subgroups

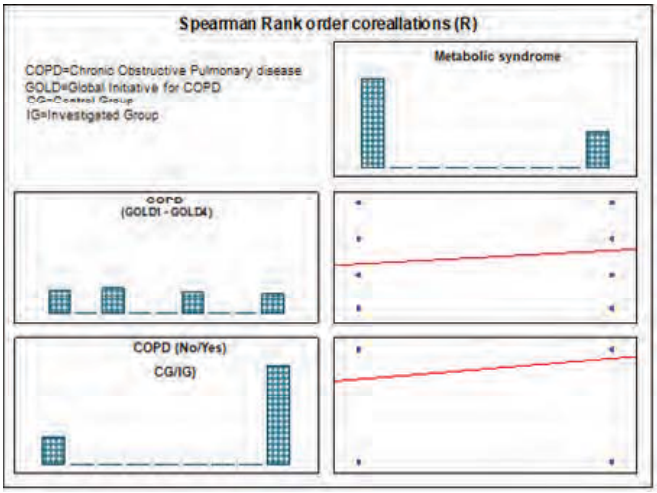

Figure 5. Predictive role of COPD for metabolic syndrome – before and after adjustment