Metabolic syndrome in hospitalized patients with chronic obstructive pulmonary disease

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Abstract

Introduction: The metabolic syndrome (MS) affects 21-53% of patients with chronic obstructive pulmonary disease (COPD) with a higher prevalence in the early stages of COPD, with results being highly variable between studies. MS may also affect natural course of COPD – number of exacerbations, quality of life and lung function.

Aim: To examine the prevalence of MS and its correlation with comorbidities and COPD characteristics in patients with COPD admitted for exacerbation.

Material and methods: 152 patients with COPD admitted for exacerbation were studied for presence of MS. All of them were also assessed for vitamin D status and diabetes mellitus type 2 (DM). Data were gathered for smoking status and exacerbations during the last year. All patients completed CAT (COPD assessment test) and mMRC (Modified Medical Research Council Dyspnea scale) questionnaires and underwent spirometry. Duration of current hospital stay was recorded.

Results: 25% of patients have MS. 23,1% of the male and 29,5% of the female patients have MS (p>0.05). The prevalence of MS in this study is significantly lower when compared to a national representative study (44,6% in subjects over 45 years). 69,1% of all patients and 97,4% from MS patients have arterial hypertension. The presence of MS is associated with significantly worse cough and sleep (1st and 7th CAT questions; p=0.002 and p=0.001 respectively) and higher total CAT score (p=0.017). Average BMI is 27,31. None of the patients have MS and BMI <25. There is a correlation between the presence of MS and DM (p=0.008) and with the number of exacerbations in the last year (p=0.015). There is no correlation between the presence of MS and the pulmonary function.

Conclusions: This study among hospitalized COPD patients finds comparable but relatively low prevalence of MS (25%) compared to previously published data (21-53%) and lower prevalence compared to general population (44,6%). MS may impact quality of life and the number of exacerbations of COPD. Having in mind that MS is more common in the early stages and decreases with COPD progression, the COPD patients admitted for exacerbation may be considered as having advanced COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with significant extrapulmonary effects that may contribute to the severity in individual patients. By 2030, COPD will be the fourth cause of mortality worldwide. The extrapulmonary comorbidities influence the prognosis of the patients with COPD (1).

Metabolic syndrome (MS) is common in patients with COPD. According to the available studies the prevalence of MS in COPD patients varies between 21-53% (2). The prevalence of MS in COPD patients is increased when compared to a control group (3-6).

Available studies suggest that MS may have impact on quality of life (7), lung function (8-12), natural course of COPD (number of exacerbations) (13,14) as well as to affect comorbidities in COPD patients (15).

Many studies examine prevalence of MS in COPD patients (3,4,6,13,16-21) with results being highly variable between studies. Prevalence of MS in an unselected Bulgarian population aged 20-80 years is 30,8%. The prevalence of MS for participants over 45 years (the most common age group for the COPD patients) is higher, 44,6% (22). An epidemiological study conducted in Bulgaria in 3598 COPD patients showed that metabolic syndrome is found in 13.8% of the patients (23). A more recent study indicates that the prevalence of metabolic syndrome is 41.8% in 141 patients with COPD compared to 39% in the control group of 103 subjects (24). The prevalence of MS in COPD patients, hospitalized for exacerbation is hard to predict because MS tends to be more prevalent in early stages of COPD while patients experiencing severe exacerbation often have advanced disease. On the other side MS may impact natural course of COPD and predispose to exacerbation which will lead to increased prevalence of MS in this group.

There is not enough data to determine whether the results from these studies are applicable to specific subgroups of patients such as COPD patients admitted for exacerbation. COPD is increasingly divided in subgroups or phenotypes based on specific features and association with prognosis or response to therapy, the most notable being the feature of frequent exacerbations (25). Presence of MS may also have distinctive characteristics for this subgroup ('severe' exacerbator phenotype). The aim of this study is to find out the prevalence of MS in patients with COPD admitted for exacerbation and the correlations of presence of MS with comorbidities and COPD characteristics.

Material and methods

A total of 152 COPD patients hospitalized for exacerbation were studied for the presence of MS, DM, and vitamin D deficiency and insufficiency using well-established criteria for:

- ❖ Presence of MS: at least 3 of the following: 1. Elevated waist circumference >102 cm in males, >88 cm in females; 2. Triglycerides >1.7 mmol/L (or on therapy); 3. HDL <1.0 mmol/L in males, <1.3 mmol/L in females (or on therapy); 4. Elevated blood pressure: systolic ≥130 and/or diastolic ≥85 mm Hg (or on therapy); 5. Fasting glucose >5.5 mmol/L (or on therapy) (26).
- ❖ Presence of DM: fasting plasma glucose ≥7.0 mmol/L OR 2-h plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT) OR HbA1c≥6.5% OR on therapy (27);

84 ❖ Presence of prediabetes: fasting plasma glucose 5.6-6.9 mmol/L OR 2-h plasma glucose
85 7.8-11.0 mmol/L during an OGTT OR HbA1c 5.7-6.4% (27);
86 ❖ Presence of vitamin D deficiency: 25(OH)D <25 nmol/L; vitamin D insufficiency:
87 25(OH)D 25-50 nmol/L; vitamin D sufficiency: >50 nmol/L (28).
88
89 The diagnosis of COPD was made according to GOLD (Global Initiative for Chronic
90 Obstructive Lung Disease) criteria (DM1). Data were gathered for age, sex, smoking status and
91 number of pack-years, number of bone fractures, therapy for arterial hypertension, therapy for
92 DM, COPD therapy and number of exacerbations in the last year. The patients completed CAT
93 and mMRC questionnaires and underwent pre- and post bronchodilatatory spirometry. Blood
94 pressure was obtained according to the American Heart Association Guidelines (29). A patient
95 was considered as having arterial hypertension if taking antihypertensives.
96 The inclusion criteria were post bronchodilator spirometry obstruction defined as
97 FEV1/FVC<0.70. All participants in this study signed informed consent.
98 The exclusion criteria were failure to comply with study procedures (no completed
99 questionnaires, no medical and demographic information, no spirometry, no lab tests) or
100 FEV1/FVC ratio >0.70 after administration of bronchodilator.
101

Smoking status

103 Every participant was classified according to smoking status (30):
104 Never smoker – never smoked a cigarette or who smoked fewer than 100 cigarettes in their
105 entire lifetime.
106 Former smoker – smoked at least 100 cigarettes in their entire life but were not currently
107 smoking.
108 Current smoker – had smoked at least 100 cigarettes in their entire life and were still smoking.
109 Numbers of pack-years were calculated using the formula:
110 Number of pack-years = years of smoking X number of daily smoked cigarettes/20
111

Anthropometric indices

113 Body weight and height were measured and the body mass index (BMI) was calculated
114 by dividing weight by height squared (kg/m^2). According to BMI all patients were classified as
115 underweight (<18,5), normal (18,5 – 24,99), overweight (25-29,99) and obese (>30). Waist
116 circumference was measured at the approximate midpoint between the lower margin of the last
117 palpable rib and the top of the iliac crest according to the WHO STEPS protocol (31). Hip
118 circumference was measured around the widest portion of the buttocks (31). Body adiposity
119 index (BAI) was calculated as:
120 *Hip circumference (in cm)/ (Height (in m) X √Height) – 18*
121

COPD exacerbations and duration of hospital stay

123 Data were gathered for number of severe exacerbations (hospitalizations) and moderate
124 exacerbations (antibiotic or/and systemic steroid treatment without hospitalization due to
125 worsening of pulmonary symptoms) (1) in the previous year. The duration of the current hospital
126 stay was recorded.

127

Quality of life

Quality of life was assessed with the mMRC scale and CAT questionnaire. Patients were instructed that there were no right or wrong answers. All patients' questions were answered. Patients were classified according to GOLD as having less symptoms (CAT <10) and breathlessness (mMRC grade 0-1) and more symptoms (CAT ≥10) and breathlessness (mMRC grade ≥2). Because all patients were hospitalized due to exacerbation there were only group C (high risk, less symptoms) and group D (high risk, more symptoms) patients according to GOLD (1).

136

Pulmonary Function Testing

The spirometry was performed using Minispir® New spirometer (MIR - Medical International Research, Italy). Patients were instructed to withdraw using short-acting β2-agonists at least 6 hours, long-acting β2-agonist at least 12 hours, long acting muscarinic antagonist 24 hours and short acting muscarinic antagonist 12 hours before the spirometry (32). Post bronchodilator spirometry testing was performed 15-30 min after inhalation of 400mcg Salbutamol according to ERS/ATS recommendations (32). Pre- and post- values were obtained for: FVC, FEV1, FEV1/FVC, FEV6, FEV1/FEV6, PEF, FEF2575, FEV3, FEV3/FVC as well as the difference between post/pre values (delta values). GLI (Global Lungs Initiative) predicted values were used (GLI-2012). Patient's obstruction was classified according to the severity of airflow limitation based on post-bronchodilator FEV1 as follows: mild (≥80% predicted); moderate (80>FEV1≥50% predicted); severe (50%>FEV1≥30% predicted); very severe (<30% predicted) (1).

150

Blood samples and analyses

A venous blood sample was collected from each subject after a 12-hour fasting. Blood samples were taken as late as possible before discharging (usually on 6th or 7th day). Plasma glucose, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol (tChol) were measured with a Roche COBAS INTEGRA® 400 plus analyzer and an enzymatic colorimetric assay and blood glucose was measured with an enzymatic reference method with hexokinase. Vitamin D was measured with Elecsys 2010 (Roche) and Electro-chemiluminescence immunoassay (ECLIA). Glycated hemoglobin (HbA1c) was measured with a NycoCard device and boronate affinity assay. For patients without established DM a 75g OGTT was performed with blood samples for glucose taken on first and second hour.

161

Statistical Analysis

Statistical analysis was performed with the SPSS for Windows software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and 95 Confidence intervals (95%CI) and categorical variables - as percentages. Chi-square test was used to determine the associations between categorical variables. Continuous variables were examined for normality by Shapiro-Wilk test. For normally distributed variables,

168 differences between the groups were determined by independent-samples T test for two samples
169 and analysis of variance (ANOVA) for more than 2 samples. Mann-Whitney U test was used for
170 abnormally distributed variables with 2 samples and Kruskal-Wallis test for variables with more
171 than 2 samples. Regression analyses were used to determine risk factors for presence of MS or
172 the consequences of having MS. Significance value (p-value) was set at 0.05.
173
174 All patients signed informed consent. Medical University-Sofia Research Ethics
175 Commission approved the study (#2976/2014).
176

Results

Sample characteristics

179 A total of 152 COPD patients admitted for exacerbation were recruited from University
180 Specialized Hospital for Active Treatment of Pulmonary Diseases 'Saint Sofia', Sofia, Bulgaria.
181 Mean age of patients in this study was 65±10 years. 71,1% (108/152) were males, 28,9%
182 (44/152) were females; mean post-bronchodilator FEV_1 was 55,3 ±19,5%. 15,8% from the
183 patients were never smokers, 57,9% - former smokers and 26,3% - current smokers. 127 patients
184 (83,6%) were receiving inhalatory corticosteroids.
185

Prevalence of MS

187 25,0% (38/152) of the patients have MS. 23,1% (25/108) of males have MS vs. 29,5%
188 (13/44) of females but this difference is not statistically significant (table 1). Mean age does not
189 differ between the patients with and without MS.
190 Fulfilled criteria for MS (in all and in MS patients) are shown in table 2. Virtually all
191 (37/38) patients with MS in this study have arterial hypertension, followed by elevated waist
192 circumference (33/38). Arterial hypertension has greatest sensitivity for predicting presence of
193 MS, but is not specific. Elevated waist circumference has greatest accuracy, defined as sum of
194 true results (true positives and true negatives) divided by total number of cases. Number of
195 fulfilled criteria in all patients is given in table 3.
196
197
198

Lifestyle factors

200 Our study did not find significant differences in prevalence of MS according to smoking
201 status and number of pack-years. Treatment with inhalatory corticosteroids (ICS) is not risk
202 factor for MS. Fasting glucose level are not influenced by ICS (all p>0.05) (table 1).
203

Comorbidity

205 In our study vitamin D levels do not significantly differ in relation to presence of MS
206 (32,11 vs 31,92 nmol/l). Presence of MS is also not related to vitamin D status (table 1).

207 Number of fractures in our study does not significantly differ regarding the presence of
208 MS. Presence of at least one fracture also does not differ significantly in relation to presence of
209 MS.
210 In our study there is a correlation between the presence of MS and DM. 52,6% (20/38)
211 from patients with MS have DM. BMI and BAI differ significantly according to presence of MS
212 – 32,51 vs 25,58, for BMI and 31,01 vs 25,58, for BAI. There is also significant difference in
213 prevalence of MS in BMI and BAI groups (table 1). It is notable that none of the patients have
214 MS and BMI <25 (table 1).
215 Linear regression showed presence of MS as risk factor for higher BMI (R=0.542,
216 r^2=0.293, p<0.0005, B=6.928, 95% CI 5.193-8.662) and BAI (R=0.406, r^2=0.165, p<0.0005,
217 B=5.423, 95% CI 3.455-7.392).
218 A logistic regression analysis was conducted to predict presence of MS in a relation to
219 presence of other comorbidities. Presence of DM slightly improves the model (chi square =
220 6.818, p=0.009 with df = 1). Nagelkerke's R2 of 0.065 indicates a weak relationship. Odds ratio
221 was 2,73. Vitamin D status does not improve the model (p>0.05).
222

Exacerbations and duration of hospital stay

224 Our study found a significant difference between the number of total exacerbations according to
225 the presence of MS (table 4, p=0.015). The number of severe exacerbation, moderate
226 exacerbation and duration of hospital stay did not reach significance.
227 Triglycerides and blood glucose levels in our study did not correlate with number of
228 exacerbations.
229 Linear regression showed presence of MS as risk factor for higher number of
230 exacerbations (R=0.207, r^2=0.043, p=0.010, B=0.596, 95% CI 0.143-1.050). From the MS
231 components presence of arterial hypertension is strongest risk factor for exacerbation (R=0.228,
232 r^2=0.052, p=0.005, B=0.615, 95% CI 0.192-1.038).
233

Quality of life

235 The presence of MS is associated with significantly worse cough and sleep (1st and 7th CAT
236 questions; p=0.002 and p=0.001 respectively) and higher total CAT score (p=0.017) (table 5).
237 However prevalence of MS is not significantly different between patients with less symptoms
238 (CAT 0-9) and breathlessness (mMRC 0 or 1) compared to patients with more symptoms (CAT
239 ≥10) and breathlessness (mMRC ≥2) (table 1).
240 Regression analyses also showed that MS is a risk factor for reduced quality of life, measured
241 with total CAT score (R=0.205, r^2=0.042, p=0.011, B=3.711, 95% CI 0.859-6,562). Presence of
242 MS also impairs cough and sleep – first (R=0.285, r^2=0.081, p<0.0005, B=0.684, 95% CI 0.313-
243 1,055) and seventh (R=0.268, r^2=0.072, p=0.001, B=0.930, 95% CI 0.390-1,470) CAT
244 questions.

Pulmonary function test (PFT)

246 Our study did not find differences in FVC, FEV1, FEV1/FVC, FEV6, FEV1/FEV6, PEF,
247 FEF2575 and FEV3 according to the presence of MS. It should be noted that there is tendency
248 for FVC and FEV1/FVC ratio. However, because of this there is significant difference in
249 FEV3/FVC ratio (table 6).

250   Regression analyses also showed that MS is not a risk factor for reduced pulmonary
251 function. However some of the components of MS are associated with reduced pulmonary
252 function with highest impact of HDL on FVC (R=0.183, r^2=0.033, p=0.024, B=-8.517, 95% CI -
253 15.904;-1,130) and FEV1 (R=0.251, r^2=0.063, p=0.001, B=-10.391, 95% CI -16.865;-3,918).
254 Fasting glucose is associated with increased FEV1/FVC ratio (R=0.186, r^2=0.035, p=0.022,
255 B=1.238, 95% CI 0.183; 2.294) probably because of lowering FVC.
256   There is no difference in prevalence of MS in patients with FEV1 <50%, when compared
257 to patients with FEV1 >50% or regarding GOLD stage (table 1).
258

Discussion

260   This study found comparable but relatively low prevalence of MS compared to previous
261 studies (table 7) (fig. 1). The prevalence of MS in our study is significantly lower when
262 compared to the general Bulgarian population (44,6% in subjects over 45 years) (22). The odds
263 ratio for COPD patients admitted for exacerbation of having MS is 0.41 compared to general
264 population (95% CI 0.28-0.61, p<0.0005).
265   Two Bulgarian studies examined the prevalence of MS in COPD patients. An
266 epidemiological study conducted in Bulgaria in COPD patients reported a prevalence of 13,8%.
267 These results differ significantly from the literature data probably because of the different
268 criteria for metabolic syndrome (presence of DM, BMI >30 and blood pressure >140/90 mmHg)
269 which makes data comparing irrelevant (23). A more recent study indicates that the prevalence
270 of metabolic syndrome is 41.8% in patients with COPD . However this study was not conducted
271 using a random sample (exclusion criteria was presence of DM, people were aged 49-79 years
272 for patients with COPD and 35-65 years for controls) (24). Nonetheless it uses similar criteria
273 for MS and when comparing the results our study finds lower prevalence of MS.
274   The prevalence results could be explained with differences between the populations in
275 different studies (physical activity, diet, lifestyle etc.). For example, Bulgaria is low-income
276 country, which may impact diet preferences and treatment choices. Furthermore, patients in this
277 study had been hospitalized due to exacerbation, which represents the most severe group of
278 COPD patients. Having in mind that MS is more common in the early stages and decreases with
279 COPD progression (21), COPD patients hospitalized for exacerbation may be considered as
280 having advanced COPD.

281 According to NHANES III study smokers are more likely to develop MS than
282 nonsmokers in general population and the risk increases with the number of pack-years even
283 after adjusting for covariates (33). Our study did not find significant differences in prevalence of
284 MS according to smoking status and number of pack-years. These results could be explained
285 with smoke being the biggest factor in developing COPD and effect of developing MS could be
286 reduced. Moreover nicotine may be an appetite suppressant and lower the weight thus decreasing
287 prevalence of metabolic syndrome (34). Third, hospitalized COPD patients are patients with
288 predominantly advanced disease and prone to cachexia and wasting. Also lifestyle changes (quit
289 smoking) in the presence of the two diseases should be considered which may change the
290 prevalence of MS.
291 Treatment with inhalatory corticosteroids (ICS) is not risk factor for MS similar to
292 findings for DM (35) and fasting glucose level are not influenced by ICS.
293 COPD is a disease that affects mainly the lungs, but is characterized by systemic
294 inflammation and a number of extrapulmonary manifestations. Only 1/3 of patients with COPD
295 die due to respiratory failure. Main cause of death is lung cancer and cardiovascular
296 complications (36).
297 The vast majority of patients with COPD have a vitamin D deficiency (37). Aside from
298 its role in the metabolism of calcium and phosphorus, vitamin D is involved in the pathogenesis
299 of multiple diseases, including MS, mainly because it affects the secretion and the function of
300 insulin (38). However in our study vitamin D levels do not significantly differ in relation to
301 presence of MS. Presence of MS is also not related to vitamin D status.
302 There are no studies that examine the relationship between osteoporosis and MS in
303 patients with COPD. However, both diseases share common risk factors such as smoking, lack
304 of physical activity, and treatment with corticosteroids. Some of the components of the
305 metabolic syndrome (arterial hypertension, elevated triglycerides, reduced HDL cholesterol) are
306 risk factors for low bone density. Systemic inflammation in MS plays a role in the pathogenesis
307 of osteoporosis (39). On the other hand, studies examining the relationship between MS and
308 osteoporosis showed inconsistent results, probably due to the protective effect of obesity (40).
309 However number of fractures in our study does not significantly differ regarding the presence of
310 MS. Presence of at least one fracture also does not differ significantly in relation to presence of
311 MS.
312 Most patients with DM have MS, but the opposite is not necessarily true (41). The
313 presence of MS in this study is associated with presence of DM, higher BMI and BAI.
314 Hyperglycemia is associated with elevated glucose concentrations in tissues and
315 bronchial aspirates where it may stimulate infection by enhancing bacterial growth and by
316 promoting bacterial interaction with the airway epithelium (42). Hyperglycemia also impairs
317 both innate and adaptive immunity, suppressing the host response to infection.
318 The presence of MS in patients with COPD increases the frequency of exacerbations (2.4
319 vs. 0.7) and their duration – (7.5 vs. 5.0 days) according to Kupeli et al. (13), and 8 versus 5.5
320 days, according to Abdelghaffar et al. (14). Our study found a significant difference between the
321 number of total exacerbations according to the presence of MS. However the number of severe
322 exacerbation, moderate exacerbation and duration of hospital stay did not differ significantly.
323 Triglycerides and blood glucose levels in our study did not correlate with number of
324 exacerbations as reported by other authors (13).
325 The presence of MS is associated with significantly worse cough and sleep and higher
326 total CAT score. This confirms the data about reduced quality of life in patients with MS (7).

327 However prevalence of MS is not significantly different between patients with less symptoms
328 (CAT 0-9) and breathlessness (mMRC 0 or 1) compared to patients with more symptoms (CAT
329 ≥10) and breathlessness (mMRC ≥2). These mixed results may be explained with COPD having
330 higher negative impact on quality of life than MS (physical limitation due to shortness of breath)
331 like suggested for DM (43) and ameliorating the effect in patients having both diseases.
332 COPD is characterized by airflow obstruction, which is not fully reversible. MS is
333 associated with a reduction of lung volumes (8-12). It should be noted that some studies found
334 no association between lung function and the presence of MS (44). MS in our study is not
335 associated with worsen pulmonary function. There is also no difference in prevalence of MS in
336 patients with FEV1 <50%, when compared to patients with FEV1 >50% or regarding GOLD
337 stage.
338

Conclusions

339

340 This study finds 25% prevalence of MS in COPD patients admitted for exacerbation
341 which is significantly lower than general population. MS is more prevalent in females, but the
342 gender difference is not statistically significant. In this study most of the patients are former
343 smokers and prevalence of MS does not differ regarding smoking status and treatment with ICS.
344 The presence of MS is associated with presence of DM, higher BMI and BAI, more
345 exacerbations during the previous year and lower quality of life. MS is not associated with
346 increased hospital stay and lower pulmonary function.
347 This study finds comparable but relatively low prevalence of MS compared to previously
348 published data (21-53%). Having in mind that MS is more common in the early stages and
349 decreases with COPD progression, the COPD patients admitted for exacerbation may be
350 considered as having advanced COPD.
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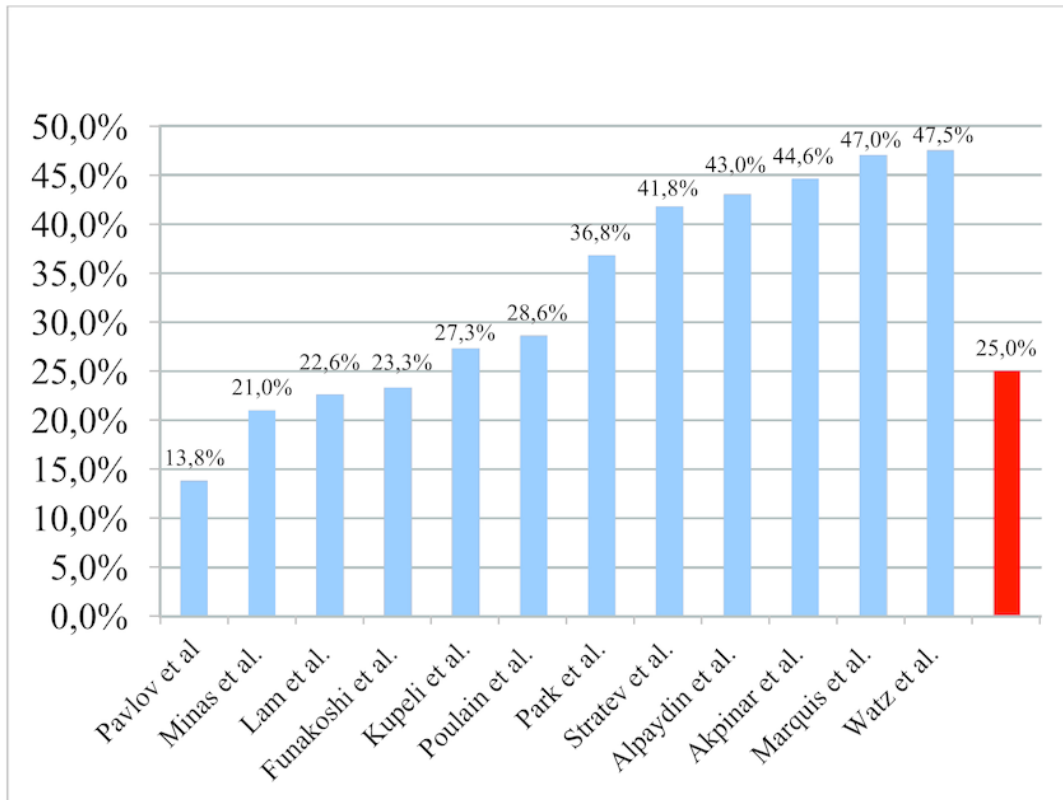
Prevalence of MS in COPD patients

Prevalence of MS according to different factors

	% MS	P value
All	25,0	
Sex		
Male	23,1	P=0.409
Female	29,5	
Smoking status		
Never	25,0	P=0.678
Former	27,3	
Current	20,0	
ICS use		
Yes	25,2	P=0.899
No	24,0	
Arterial hypertension		
Yes	35,2	**P<0.0005**
No	2,1	
Vitamin D status		
>50 nmol/l	24,2	P=0.929
25-50 nmol/l	24,6	
<25 nmol/l	28,0	
DM		
Yes	37,7	**P=0.008**
No	18,2	
BMI		
Underweight	0	**P<0.0005**
Normal	0	
Overweight	27,3	
Obese	54,8	
BAI		
Underweight	0	**P=0.001**
Normal	17,5	
Overweight	28,9	
Obese	50,0	
Quality of life		
CAT 0-9	16,0	P=0.256
CAT ≥10	26,8	
mMRC 0 or 1	18,9	P=0.201
mMRC ≥2	28,3	
FEV1		
FEV1≥50%	21,3	P=0.390
FEV1<50%	27,5	
FEV1≥80%	11,8	P=0.852
80%>FEV1≥50%	28,8	
50%>FEV1≥30%	26,1	
FEV1<30%	25,0	

Fulfilled criteria for MS

MS criteria	All patients (n=152)	MS only (n=38)	Without MS (n=114)	Accuracy
Elevated blood pressure: systolic ≥130 and/or diastolic ≥85 mm Hg (or on therapy)	69,1% (n=105)	97,4% (n=37)	59,6% (n=68)	54,6%
Elevated waist circumference >102 cm in males, >88 cm in females	28,3% (n=43)	86,8% (n=33)	8,8% (n=10)	90,1%
Triglycerides >1,7 mmol/L (or on therapy)	29,6% (n=45)	60,5% (n=23)	19,3% (n=22)	75,7%
Fasting glucose >5,5 mmol/L (or on therapy)	34,2% (n=52)	65,8% (n=25)	23,7% (n=27)	73,7%
HDL <1.0 mmol/L in males, <1.3 mmol/L in females (or on therapy)	15,8% (n=24)	39.5% (n=15)	7,9% (n=9)	78,9%

Number of fulfilled criteria for MS in all patients

Number of fulfilled criteria	%	n
0	13,8	21
1	33,6	51
2	27,6	42
3	13,2	20
4	10,5	16
5	1,3	2

Number of exacerbations in previous year and duration of hospital stay

	No MS	MS
Moderate exacerbations	0,61 (0,49-0,76)	0,92 (0,59-1,34)
Severe exacerbations	1,79 (1,61-1,97)	2,08 (1,71-2,50)
All exacerbations	**2,40 (2,19-2,61)**	**3,00 (2,56-3,52)**
Hospital stay (in days)	7,47 (7,24-7,70)	7,63 (7,28-8,05)

Mean CAT score on every question and in total according to presence of MS

MS	Mean CAT score	N	P value
MS – no	CAT1 1,95	114	**P=0.002**
MS - yes	CAT1 2,63	38	
MS – no	CAT2 1,92	114	P=0.063
MS - yes	CAT2 2,34	38	
MS – no	CAT3 2,54	114	P=0.092
MS - yes	CAT3 2,97	38	
MS – no	CAT4 3,52	114	P=0.361
MS - yes	CAT4 3,74	38	
MS – no	CAT5 1,23	114	P=0.198
MS - yes	CAT5 1,66	38	
MS – no	CAT6 1,54	114	P=0.695
MS - yes	CAT6 1,68	38	
MS – no	CAT7 1,28	114	**P=0.001**
MS - yes	CAT7 2,21	38	
MS – no	CAT8 2,62	114	P=0.068
MS - yes	CAT8 3,08	38	
MS – no	Total CAT 16,61	114	**P=0.017**
MS - yes	Total CAT 20,32	38	

Mean PFT values

MS	Mean PFT value	N	P value
No	FEV1 55,56%	114	P=0.811
Yes	FEV1 54,68%	38	
No	FVC 80,46%	114	P=0.094
Yes	FVC 72,45%	38	
No	FEV1/FVC 0,53	114	P=0.091
Yes	FEV1/FVC 0,57	38	
No	FEV6 73,89%	114	P=0.277
Yes	FEV6 68,63%	38	
No	FEV1/FEV6 0,57	114	P=0.107
Yes	FEV1/FEV6 0,61	38	
No	PEF 55,62%	114	P=0.735
Yes	PEF 56,66%	38	
No	FEF2575 38,89%	114	P=0.316
Yes	FEF2575 40,95%	38	
No	FEV3 66,62%	114	P=0.601
Yes	FEV3 63,89%	38	
No	FEV3/FVC 0,81	114	**P=0.033**
Yes	FEV3/FVC 0,85	38	

Prevalence of MS in patients with COPD

Authors	N	Studied population	Prevalence of MS
Akpinar et al. (16)	133	Patients with COPD and controls	**44.6%**
Funakoshi et al. (3)	7189	Men aged 45-88 years	**16.8%**, OR 0.72 (95% CI 0.51-1.02) in GOLD I; **28.7%**, OR 1.33 (95% CI 1.01-1.76) in GOLD II-IV
Kupeli et al. (13)	106	Hospitalized patients with COPD	**27.3%**
Lam et al. (4)	7358	General population >50 years	**22.6%**; OR 1.47 (95% CI 1.12-1.92)
Marquis et al. (17)	72	Patients with COPD and controls	**47%**
Minas et al. (18)	114	Men with COPD	**21%**
Ozgen Alpaydin et al. (19)	90	Patients with COPD and controls	**43%**
Park et al. (6)	1215	Patients with COPD and controls >40 years	**33%** vs 22.2% for men; **48.5%** vs 29.6% for women OR 2.03 (95% CI 1.08-3.80)
Poulain et al. (20)	28	Patients with COPD	Overweight – **50%**; Normal weight – **0%**.
Watz et al. (21)	200	Patients with COPD and chronic bronchitis	GOLD I – **50%**; GOLD II – **53%**; GOLD III – **37%**; GOLD IV – **44%**; Chronic bronchitis – 53%