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The Association Between Comorbidities and a High-Risk Status According to COPD GOLD Groups

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Objective: The natural course of the chronic obstructive pulmonary disease (COPD) is thought to be affected by the severity of COPD, frequency of episodes, as well as the presence of comorbid conditions. It was aimed to explore the effect of comorbid conditions on high-risk status in stable COPD patients.

Material and methods: Study participants consisted of stable COPD patients attending to the pulmonology outpatient unit of a tertiary center between 15th May 2018 and 12th Dec 2019. Demographic data, comorbidities, clinical index scores, modified Charlson comorbidity index score (mCCI), BODE index score, and the Short Form 36 (SF-36) scores as a generic life quality measure were recorded. Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups were determined based on symptoms and exacerbations.

Results: There were 23(25.8%), 31(34.8%), 2(2.2%), and 33(37.1%) patients in GOLD gropus A, B, C, and D, respectively. Among these, A and B groups are considered as low-risk, and C and D groups are considered as high-risk. High risk patients had higher mCCI (p < 0.001) and were more likely to have hypertension (p=0.012), congestive cardiac failure (p=0.029), chronic renal failure (p=0.022), osteoporosis (p=0.001), and anemia (p<0.001). In a logistic regression analysis performed to examine the determinants of high-risk status in COPD-GOLD groups, biomass exposure was found to increase the likelihood of having a high risk-status by 3-fold.

Conclusion: Classification of stable COPD patients according to GOLD groups showed higher mCCI in subjects with high-risk status. Comorbidities and mCCI did not appear to affect the high-risk status. Biomass exposure was associated with an increased risk of having a high-risk status.

Keywords: chronic obstructive pulmonary disease, global initiative for chronic obstructive lung disease groups, comorbidity, biomass exposure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable condition that is generally caused by significant exposure to noxious particles or gases and that is characterized by persistant airflow obstruction and respiratory symptoms [1]. Globally, COPD now represents the third common leading cause of death [1]. Although lungs represent the initial site of involvement, COPD is generally considered a complex multi-faceted disorder characterized by chronic systemic inflammation and common occurrence of comorbidities [2,3]. COPD severity, frequency of exacerbations, and presence of comorbidities are known to be associated with symptom severity and worsening of the disease [4,5]. In COPD patients, comorbid conditions have a major impact on the quality of life, frequency of exacerbations, and survival [1,2]. Although the mechanisms have not been defined yet, there are studies indicating that there is a chronic inflammatory condition that accelerates the natural history of some comorbidities in COPD. COPD and other comorbidities are actually considered part of the systemic disease [6,7] .

The objective of this study is to examine the association between comorbidities and GOLD groups among clinically stable COPD patients, and to determine the factors that are more commonly observed among high-risk patients versus low-risk patients. To the best of our knowledge, this is one of the few studies to evaluate the association between comorbidities and GOLD groups in COPD patients.

METHODS

COPD patients who have been admitted between 15th May 2018 and 12th Dec 2019 to the Pulmonology Outpatient Clinics of Hacettepe University, a tertiary care center in Ankara, the capital city of Turkey with a population of around 5.5 million, were investigated for eligibility. Adult patients ≥40 years of age diagnosed with stable COPD according to GOLD 2017 guidelines and who gave consent were included. In order to be eligible, patients had to have a post-bronchodilator FEV1/FVC ratio of < 0.7 (Forced Expiratory Volume at 1 second/ Forced Vital Capacity). In this cross-sectional study, data regarding demographic features, COPD symptoms, and comorbid conditions were collected with a survey. Diagnosis of comorbidities was based on self-report and hospital electronic records. Pulmonary function test results and data that was necessary to calculate the clinical index scores were obtained from hospital electronic records. The body mass index (BMI) was calculated using height and weight of each patient, and was classified according to the World Health Organization (WHO) scheme [8]. The Modified Medical Research Council Dyspnea Scale (mMRC), and the Chronic Obstructive Pulmonary Disease Asssessment Test (CAT) were used to assess the sypmtoms (1). Patients were classified as of GOLD 2017 guideline groups A, B, C, and D COPD.

SF-36
This generic tool for measuring the quality of life includes 8 sections, each containing 2 to 10 items (general health, physical functioning, physical role, emotional role, social functioning, pain, energy, and mental health), each of which is scored in one section only. The score for the scales ranges between 0 and 100, higher scores showing better quality of life [9].

Pulmonary Function Tests
Spirometry tests were carried out according to the European Respiratory Society (ERS) standards, and included FVC and FEV1. Also, the FEV1/FVC ratio was calculated [10,11].

COPD Symptom Assessment Tools
mMRC and CAT were used for symptom assessment. The estimated risk of mortality was calculated using the BODE (Body-mass index, airflow Obstruction, Dyspnea, Exercise) index [1].

Modified Charlson Comorbidity Index
A total of 19 different comorbidities and cancer diagnoses were inquired and scored using the Modified Charlson Comorbidity Index (mCCI). An additional 1-point was added to the current score for each 10 years after age 40, yielding the mCCI score [12,13].

Exercise Performance
In line with the American Thoracic Society (ATS) protocol, the 6-minute walking distance (6-

MWD) was measured. After an initial assessment for potential contraindications using oxygen saturation, pulse, and blood pressure, selected patients underwent the protocol. The severity of dyspnea before and after the procedure was evaluated with modified BORG scale [14].

Ethical Considerations

The study protocol was approved by the Ethics Committee of Hacettepe University for Non-Interventional Clinical Research on 19th Nov 2019 (no. 2019/27-16), and the study was conducted according to ethical principles set forth in Helsinki Declaration. All participants provided written informed consent. No financial support was obtained for the study, and the study authors declared no conflicts of interest. The study results were discussed as an oral presentation at the 25th Annual Congress of the Turkish Thoracic Society that was held between 24th and 28th of May 2022 in Antalya, Turkey [SS-037].

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation or median (interquartile range) for normally distributed or non-normally distributed continuous variables and as n (frequency percentage) for categorical variables.

Differences between groups were assessed by Student's t-test for normally distributed continuous variables and by Mann–Whitney U test for non-normally distributed continuous variables. Comparisons of categorical variables were carried out by Chi-square test or Fisher's exact test and odds ratio, and its 95% confidence intervals were given as effect size.

A multivariable logistic regression model was built to determine the association between high-risk COPD and modified Charlson Comorbidity Index scores, with adjustment for age, gender, presence of pre-obesity or obesity, current smoking status, and biomass exposure. For the model selection, enter method (based on the likelihood ratio) was used. Model fit was evaluated with the Hosmer-Lemeshow goodness-of-fit test.

All statistical tests were two-tailed, and statistical significance was set at $p<0.05$. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 23 (IBM, Armonk, NY, USA).

RESULTS

All eligible patients (n=89) provided informed consent and were included in the statistical analyses. Of these 23 (25.8%), 31 (34.8%), 2 (2.2%), and 33 (37.1%) were in GOLD groups A, B, C, and D, respectively. On average, high-risk patients were 8 years older than low-risk patients. Although majority of the patients were male, male predominance was even more marked (87.0%) in the low-risk group.

The patients reported at least one comorbidity were 79.6% in low-risk group and 91.4% in high-risk group (p=0.15). The mean mCCI scores (± SD) in high-risk and low-risk patients were significantly different (6.7 ± 2.72 versus 4.7 ± 2.56, respectively; $p < 0.001$). Similarly the median number [IQR] of comorbidities showed a significant difference between low-risk and high-risk patients (2.0 [3.0] versus. 5.0 [5.0]; p=0.001). There was no statistically significant difference between high and low risk patients in terms of presence of diabetes mellitus (p=0.86), obstructive sleep apnea syndrome (p=0.076), bronchiectasis (p=0.22), and malignancy (p=0.90). Hypertension (p=0.012), congestive heart disease (p=0.029), chronic renal failure (p=0.022), osteoporosis (p=0.001) and anemia (p<0.001) were more common in the high-risk group than in the low-risk group, and the difference was statistically significant (Table 1).

Biomass exposure was significantly higher among high-risk patients (62.9%) as compared to low risk (37.0%) patients. Table 1 shows the demographic characteristics, comorbidities, disease burden, clinical parameters, and scores according to GOLD groups.

Table 2 shows SF-36 results according to GOLD groups. In all 8 sections of SF-36, high-risk patients had significantly lower quality of life scores as compared to low-risk patients.

The treatments received by the patients included long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) and LABA + ICS combined preparations, short acting inhaler, and systemic theophylline. No patients received systemic steroids or roflumilast. Table 3 shows the distribution of treatments according to GOLD groups.

Age, gender, BMI were included as potential confounders, and current smoking (a proven risk

factor for high-risk COPD) and biomass exposure were included as covariants in a logistic regression model built to assess the relationship between mCCI scores and high-risk COPD status. Model fit was evaluated with the Hosmer-Lemeshow goodness-of-fit test (p=0.79). Nagelkerke's R2 of the model was 0.300. Subsequently, the modified CCI score lost its significance in the model. Biomass exposure 3.08 times increased the status of being in the high-risk GOLD group (95% CI = 1.10-8.62; p=0.033) (Table 4).

Table 1. Demographic characteristics, comorbid conditions, and disease severity according to COPD GOLD groups

Variable	Overall (n= 89)	High Risk Groups C and D (n= 35)	Low Risk Groups A and B (n= 54)	OR (95% CI)	P-value
Demographics					
Age, y	66.3 ± 10.58	71.0 ± 9.60	63.2 ± 10.12	-	**<0.001**
Male	70 (78.7)	23 (65.7)	47 (87.0)	0.29 (0.01-0.82)	**0.016**
BMI, kg/m²	27.1 ± 5.84	26.4 ± 6.45	27.5 ± 5.42	-	0.38
Current smoker	78 (87.6)	26 (74.3)	52 (96.3)	0.11 (0.02-0.55)	**0.006***
Biomass exposure	42 (47.2)	22 (62.9)	20 (37.0)	2.88 (1.19-6.94)	**0.017**
Long-term oxygen therapy	27 (30.3)	20 (57.1)	7 (13.0)	8.95 (3.17-25.29)	**<0.001**
Use of nebulizer	27 (30.3)	19 (54.3)	8 (14.8)	6.83 (2.50-18.62)	**<0.001**
Non-invasive mechanical ventilation	11 (12.4)	6 (17.1)	5 (9.3)	2.03 (0.57-7.24)	0.33
Allergy	10 (11.2)	4 (11.4)	6 (11.1)	1.03 (0.27-3.96)	1.00*
Comorbidities	75 (84.3)	32 (91.4)	43 (79.6)	2.73 (0.70-10.59)	0.15
Diabetes mellitus	22 (24.7)	9 (25.7)	13 (24.1)	1.09 (0.41-2.91)	0.86
Hypertension	49 (55.1)	25 (71.4)	24 (44.4)	3.13 (1.26-7.75)	**0.012**
Obstructive sleep apnea syndrome	5 (5.6)	-	5 (9.3)	-	0.076*
Congestive heart failure	22 (24.7)	13 (37.1)	9 (16.7)	2.96 (1.10-7.96)	**0.029**
Chronic renal failure	11 (12.4)	8 (22.9)	3 (5.6)	5.04 (1.23-20.56)	**0.022***
Bronchiectasis	11 (12.4)	6 (17.1)	5 (9.3)	2.03 (0.57-7.24)	0.22*
Malignancy	17 (19.3)	7 (20.0)	10 (18.9)	1.08 (0.37-3.16)	0.90
Osteoporosis	26 (29.2)	17 (48.6)	9 (16.7)	4.72 (1.78-12.53)	**0.001**
Anemia	44 (49.4)	27 (77.1)	17 (31.5)	7.35 (2.77-19.49)	**<0.001**
Charlson comorbidity index score	5.45 ± 2.79	6.7 ± 2.72	4.7 ± 2.56	-	**<0.001**
COPD severity					
BODE Index	3.0 [5.0]	8.0 [4.0]	2.0 [2.0]	-	**<0.001**
0-2 (reference)	34 (38.2)	2 (5.7)	32 (59.3)	1.00	**<0.001**
3-4	17 (19.1)	2 (5.7)	15 (27.8)	2.13 (0.28-16.63)	
5-6	13 (14.6)	9 (25.7)	4 (7.4)	36.0 (5.65-229.3)	
7-10	25 (28.1)	22 (62.9)	3 (5.6)	117.3 (18.09-761)	
GOLD stage					0.006*
I. (reference)	10 (13.9)	5 (22.7)	5 (10.0)	1.00	
II.	34 (47.2)	4 (18.2)	30 (60.0)	0.13 (0.03-0.67)	
III.	22 (30.6)	10 (45.5)	12 (24.0)	0.83 (0.19-3.72)	
IV.	6 (8.3)	3 (13.6)	3 (6.0)	1.00 (0.13-7.57)	
CAT score	17.5 ± 10.45	25.8 ± 9.35	12.2 ± 7.13	-	**<0.001**
mMRC score	2.0 [3.0]	4.0 [1.0]	1.5 [1.0]	-	**<0.001**
6MWT distance, m	390.0 [381.0]	50.0 [100.0]	480.0 [183.0]	-	**<0.001**

Values are presented as mean ± standard deviation, median [interquartile range] or number (%).
6MWT = 6-minute walk test; GOLD=Global Initiative for Chronic Obstructive Lung Disease;
CAT=COPD Assessment Test; mMRC= Modified Medical Research Council Dyspnea Scale; BMI= Body Mass Index;
OR= Odds ratio, CI = Confidence interval
* Fischer's exact test p-value

Table 2. Distribution of quality of health short form-36 in COPD GOLD groups

Short form-36	Overall (n=89)	High Risk Groups C and D (n=35) Mean ± SD Median [IQR]	Low Risk Groups A and B (n=54) Mean ± SD Median [IQR]	p-value
Physical functioning	65.0 [75.0]	10.0 [30.0]	77.5 [31.0]	**<0.001**
Role limitations due to physical health	0.0 [50.0]	0.0 [0.0]	50.0 [81.0]	**<0.001**
Role limitations due to emotional problems	100.0 [100.0]	0.0 [100.0]	100.0 [75.0]	**<0.001**
Energy/fatigue	50.0 [30.0]	40.0 [35.0]	60.0 [31.0]	**<0.001**
Emotional well-being	64.0 [22.0]	60.0 [36.0]	66.0 [22.0]	**0.014**
Social functioning	62.5 [75.0]	25.0 [25.0]	87.5 [37.5]	**<0.001**
Pain	100.0 [22.5]	100.0 [55.0]	100.0 [152.5]	**0.001**
General health	49.9 ± 20.46	37.9 ± 16.06	57.7 ± 19.30	**<0.001***

SD: Standard deviation, IQR: Interquartile range

*Student's t-test

Table 3. Distribution of treatment in COPD-GOLD groups

Treatment	Overall patient (n=89) n (%)	Groups C and D (n=35) n (%)	Groups A and B (n=54) n (%)	OR (95% CI)	p-value
Inhalers					
Any short-acting	27 (30.3)	17 (48.6)	10 (18.5)	4.16 (1.60-10.79)	**0.003**
LABA only	5 (5.6)	-	5 (9.3)	-	0.076*
LAMA only	36 (40.4)	16 (45.7)	20 (37.0)	1.43 (0.60-3.40)	0.42
LABA+LAMA	7 (7.9)	1 (7.9)	6 (11.1)	0.24 (0.03-2.05)	0.16*
LABA+ICS	45 (50.6)	19 (54.3)	26 (48.1)	1.28 (0.55-3.00)	0.57
Systemic medications					
Theophylline	4 (4.5)	3 (8.6)	1 (1.9)	4.97 (0.50-49.8)	0.17*

OR = Odds ratio, CI = confidence interval, LABA = Long-acting beta 2 agonist, LAMA = Long-acting muscarinic antagonist, ICS = inhaled corticosteroids

* Fischer's exact test p-value

Table 4. Results of a logistic regression analysis for determinants of high-risk status according to COPD-GOLD groups

	Univariate			Multivariate		
	crude OR	95% CI	p-value	adj OR	95% CI	p-value
Charlson Comorbidity Index score	1.33	1.12 – 1.59	0.001	1.13	0.88 – 1.43	0.34
Male gender	0.29	0.10 – 0.82	0.020	0.53	0.13 – 2.23	0.39
Age (years)	1.08	1.03 – 1.14	0.001	1.05	0.98 – 1.12	0.18
Pre-obesity and obesity (BMI >25kg/m^2)	0.81	0.34 – 1.96	0.65	0.62	0.22 – 1.76	0.37
Biomass exposure	2.87	1.19 – 6.94	0.019	3.08	1.10 – 8.62	0.033
Current smoking	0.11	0.02 – 0.55	0.007	0.55	0.08 – 4.00	0.56

OR: odds ratio, adj: adjusted, CI: confidence interval, BMI: Body-mass index

DISCUSSION

As a result of this cross-sectional study, there was no association between high-risk GOLD group and the presence of at least one comorbidity, while the number of modified CCI and reported comorbidities was higher in high-risk GOLD group. No association was found between high-risk COPD and diabetes mellitus, obstructive sleep apnea syndrome, bronchiectasis, and malignancy, while hypertension, congestive heart disease, chronic renal failure, osteoporosis, and anemia were more common in the high-risk group than in the low-risk group.

The most likely reason for the absence of a statistically significant association between the presence of at least one comorbidity and high-risk GOLD group was the high prevalence of at least one comorbid condition in all COPD patients, regardless

of risk status. Although there was no statistically-significant association, it was also found that at least one comorbid condition was more common in the high-risk group.

Modified CCI is valuable as it is a standardized indicator in the evaluation of comorbid condition. The mean mCCI was 2 points higher in the high-risk group than in the low-risk group. Similarly, the median number of comorbidities between high- and low-risk GOLD groups was 5 and 2, respectively.

However, the statistical significance of the mCCI score was lost in the multivariate analysis, probably due to the fact that this scoring system is mainly used to predict mortality and also due to the fact that the effect of age was eliminated when adjustments for age was performed, although increased age was associated both with high-risk GOLD group and higher mCCI scores. The association between mCCI and high-risk GOLD group persisted when age was excluded from the model (OR=1.24; 95%CI=1.02 – 1.51; p=0.030). High-risk patients also had higher number of comorbidities. In a 2021 study, a mCCI score of ≥ 3 were found to be potential causes of low FEV1 in COPD patients followed-up for 1 year [15]. Also, in a study from 2018, arrhtyhmia, osteoporosis and certain other comorbidities were significantly more common in patients with GOLD groups C and D [16]. In a study conducted in the UK, in which 2620 patients who were classified as mild, moderate and severe for airway obstruction level according to the COPD-GOLD criteria, were evaluated. Especially in cardiovascular diseases (hypertension, coronary artery disease, diabetes, stroke/TIA, AF, HF) there is an increasing trend from mild to severe airway obstruction [17]. In a study conducted in Moldova between 2015 and 2017 in 435 patients, heart failure was determined with increasing frequency in 2011 COPD-GOLD B, C and D groups, but no significant difference was found in terms of hypertension and coronary heart disease [18].

Among our participants, smoking was more common in those with low-risk status. Firstly, this was a cross-sectional study providing no reliable information on past history of smoking, and this apparent paradox could be related with the fact that increasing disease burden could have led to increased quitting. In another prospective study from our country involving 463 COPD patients, current smoking was found to be less common in

GOLD group C and D patients, as compared to those in GOLD groups A and B, similar to our findings [19]. In a 2017 study by Sun et al. classifying patients according to GOLD 2017 guidelines, the current smoking rate was also shown to decreasing trend among GOLD groups A to D. [20].

Low or high risk COPD patients according to GOLD classification did not differ significantly in terms of body mass index. Similarly, a previous study reported comparable BMI values across GOLD A, B, C, and D group patients [20]. A logistic regression analysis showed that obesity was associated with a 1.6 increased likelihood of having a low-risk status. Cachexia and underweight are associated with a worse prognosis and increased mortality in patients with severe COPD [21]. Obese patients were more likely to be in the low-risk group. It has been reported that obesity is not associated with a worsening of pulmonary functions and may have a protective effect against mortality [22]. A significantly increased risk of COPD was reported in underweight individuals versus overweight individuals [23]. Metabolic syndrome and abdominal obesity are more common in mild to moderately severe COPD patients in comparison with severe COPD patients [24].

In this study, the high-risk COPD patients were found to have higher biomass exposure than low-risk patients (p=0.017). According to a multivariate analysis, exposure to biomass exposure was associated with a 3.08-fold increased likelihood of having a high-risk COPD status. Biomass exposure is known to be particularly higher in developing countries and in rural areas [25]. In the developing world, approximately 50% of the COPD related deaths result from biomass exposure. Similarly, women with indoor exposure to smoke have been reported to be 3-times more likely to develop COPD as compared to women who cook using cleaner heat sources such as electricity and gas [26,27]. For example, in a study from Columbia, the use of biomass stoves for ≥ 10 years was associated with higher risk of COPD [26]. In another study, biomass exposure was found to be associated with reduced quality of life in COPD patients. Camp et al., observed more severe symptoms and worse clinical scores in female COPD patients with biomass exposure than in female smoker COPD patients [28]. In another study including 138 female patients with COPD and similar obstruction, reduced quality of life and

worse clinical scores were found among those with biomass exposure [26].

Increasing disease severity in the participants of this study was associated with reduced life quality scores. Also, severe COPD patients had lower quality of life scores than mild to moderately severe cases. Patients with GOLD group A and B disease were reported to have better life quality indices than in the other groups. This was explained on the basis of social isolation due to reduced mobility, which was caused by more severe disease in GOLD C and D groups [29].

Due to the cross-sectional design of our study, it is not possible to determine cause and effect relationships. Also, since it only included patients attending to an outpatient unit, the results may not be generalizable to the general population. Other factors that limit the generalizability of our observations include the single-center design and lack of random sampling. However, the internal reliability of our results may be high, as the missing data was minimal, and objective methods were used for patient assessment in addition to patients' self-reports. In any case, the recall factor should be taken into consideration for data collected on the basis of patients' reports.

In conclusion, to the best of our knowledge, this is the first study in our country investigating the association between comorbidities and COPD GOLD groups. While no associations were found between comorbidities and high-risk status, biomass exposure emerged as a significant risk factor. To better elucidate the potential associations between comorbidity and high-risk COPD status, further multi-center studies with samples more representative of the general population are warranted. Such studies may also shed more light on the dose-response relationship for biomass exposure in representative patient populations.

Conflict of interest

The authors declare that there is no conflict of interest.

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