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CLINICAL STUDY

Obesity, Charlson comorbidity index, and neutrophil-to--lymphocyte ratio in chronic obstructive pulmonary disease: relationship to disease severity

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ABSTRACT

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory lung disease with high mortality and morbidity rates. Obesity, various comorbid diseases, and inflammation often coexist in chronic obstructive pulmonary disease (COPD), exhibiting a complex interaction with disease severity. The aim of the study was to examine the relationship between COPD markers and obesity, the Charlson Comorbidity Index (CCI), and neutrophil/lymphocyte ratio (NLR).

METHODS: Eighty male patients with stable COPD admitted to the pulmonology unit were included in the study. The presence of comorbidities was investigated in obese and non-obese individuals with COPD. Pulmonary function tests and the mMRC dyspnea scale were examined, and CCI scores were calculated.

RESULTS: 60.9 % with mild/moderate COPD, and 64.7 % with severe COPD had a comorbid disease. The incidence of hypertension and diabetes was significantly higher in obese patients. The obesity rate was 41.3 % in patients with mild/moderate COPD ($FEV_1 \geq 50$) and 26.5 % in those with severe COPD ($FEV_1 < 50$). There was a positive and significant correlation between CCI value and BMI and mMRC dyspnea scale. NLR was significantly higher in patients with $FEV_1 < 50$ and mMRC ≥ 2.

CONCLUSIONS: As a result, it is essential to screen obese patients with COPD, who are among the groups with the highest incidence of comorbidities, in terms of such diseases that exacerbate the symptoms of their disease. Findings may support the potential applicability of simple blood count indices (such as NLR) in the clinical assessment of disease in stable COPD patients *(Tab. 4, Fig. 1, Ref. 46)*. Text in PDF *www.elis.sk*

KEY WORDS: COPD, obesity, Charlson comorbidity index, inflammation, neutrophil-to-lymphocyte ratio.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality and is a significant public health issue prevalence of which is expected to increase further in the coming years (1). The number of cases of comorbid obesity and respiratory disease has been increasing recently (2, 3). It is widely accepted that malnourished COPD patients with low body weight are at greater risk of exacerbations and have higher mortality rates (4, 5). Notably, however, there is evidence that individuals with COPD who are overweight or obese have a reduced risk of hospitalization and lower mortality rates. This is thought to be due to the physiological advantage of overweight or obese patients (4–6). In addition, this prognostic advantage of increased body mass index (BMI) in COPD, also called the "obesity paradox", may also be related to the direct effect of adipose tissue on lung mechanics (partial reduction in static volumes in obese COPD patients, etc.) (7). However, low lean body mass index in overweight patients means proportionally high-fat mass index. Furthermore, fat mass can spread from subcutaneous (subdermal) tissue to visceral (intra-abdominal) adipose tissue, which is characterized by increased cardiovascular risk in patients with mild to moderate COPD (8).

Many comorbid diseases are observed in patients with COPD, which can affect many systems in the body and cause an increase in morbidity and mortality. While some of the comorbid diseases develop due to long-term smoking, advanced age, and genetic factors, some develop due to the systemic effect of COPD (9). Major comorbid diseases are cardiovascular system diseases, skeletal muscle weakness, metabolic syndrome, diabetes mellitus, cachexia, osteoporosis, lung cancer, anemia, glaucoma, obstructive sleep apnea syndrome, and depression (10). Symptoms and side effects of treatments in patients with COPD complicate the

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treatment of comorbid diseases. The presence of comorbidity in the patient affects COPD treatment, severity, symptoms, number of exacerbations, disease course, and mortality (9).

It has been reported that the disease develops as a result of tissue and defense system damage together with inflammation that starts as a result of exposure to cigarette smoke and toxic gases (10). Hydrogen peroxide, superoxide anion, and hydroxyl radical are the major oxidant molecules released from cigarette smoke and neutrophils and are responsible for the pathogenesis of COPD (12). Macrophage, T lymphocyte (especially CD8+) and neutrophil cells, and protease and oxidant mediators released from them have a significant effect on inflammation (11, 12). Peripheral blood neutrophil/lymphocyte ratio (NLR) is increasingly being investigated as a systemic inflammatory marker as it can be assessed quickly, widely, and relatively inexpensively by routine blood count analysis. The disease severity in a variety of chronic diseases, including cardiovascular and renal diseases, has also been associated with hospitalization, malnutrition, relapses, and mortality (13, 14). In recent years, NLR has also been searched as a diagnostic and prognostic marker in COPD. Various biochemical markers have been studied as outcome predictors in COPD, but their measurement often requires significant time and resources. Relatively simple biomarkers of inflammation calculated through routine CBC tests, such as NLR, can also predict COPD progression (15).

In this study, it was aimed to evaluate the relationship of prognostic models such as obesity, Charlson comorbidity index and neutrophil/lymphocyte ratio and disease severity in COPD. It has been hypothesized that obesity and inflammation increase comorbid diseases in COPD and are associated with disease severity. To test this hypothesis, NLR, a composite indicator of neutrophils and lymphocytes involved in COPD inflammation, and the CCI score, which determines the level of comorbidity, were used and comorbidity differences in obese and non-obese patients were questioned.

Material and methods

Sampling and research plan

This study is a cross-sectional study and was carried out with male patients diagnosed with COPD in a stable period admitted to the pulmonary diseases' outpatient clinic of Gazi University Medical Faculty Hospital, and Atatürk Training and Research Hospital. When calculated with 5 % margin of error, 95 % confidence interval and 80 % power using the G-power 3.1.9.2 program, it was found that at least 80 people should be included in the study. Eighty patients who voluntarily agreed to participate and completed the study were included in the study. Patients who had an exacerbation in the last six weeks and those over 65 years of age were excluded from the study. Questionnaires and scales were applied to the participants by face-to-face interview method by the researchers. Anthropometric measurements of the patients were made, and body weight and fat ratio were determined by the bioelectrical impedance analysis method. The Neutrophil/Lymphocyte ratio was calculated with blood test results. The Charlson comorbidity Index score was determined according to comorbid diseases. For spirometric evaluation, pulmonary function tests of the patients were performed by the nurses on duty. The dyspnea status of the patients was evaluated using the mMRC dyspnea scale.

This study was conducted according to the guidelines laid down in the 1964 Declaration of Helsinki. For the study, "Ethics Committee Approval" with the number KN 38 and dated 25.01.2016 was obtained from the Clinical Research Ethics Committee of Gazi University Medical Faculty Hospital. All participants signed informed consent.

Anthropometric measurements and bioelectrical impedance analysis (BIA)

Height, waist, and hip circumference of all patients were taken according to the measurement technique (16). In terms of having a chronic disease risk according to the World Health Organization (WHO) classification, waist circumference measurements for male individuals are classified as < 94 cm normal, 94–102 cm risky, and ≥ 102 cm high risk. The waist-to-hip ratio of the patients was calculated, and 0.9 and above were considered to be at risk for male individuals according to the WHO classification (17). For body analysis, the BIA method and Tanita BC532 brand device were used. BMI (body weight/height^2, kg/m^2) values of the patients were calculated using weight and height measurements and BMI classification has been evaluated according to the WHO classification (underweight: < 18.5, normal: 18.5–24.9, overweight: 25.0–29.9, and obese: ≥ 30.0 kg/m^2) (18).

Biochemical tests

Analyzes were made in a private laboratory and the neutrophil, lymphocyte, monocytes, and leukocyte counts of the patients were checked. The neutrophil/lymphocyte ratio was calculated as a marker of inflammation.

The Charlson comorbidity index (CCI)

The Charlson comorbidity index is a method developed to determine the level of comorbidities that can increase the risk of mortality. Among the 19 diseases in this index, a total score is formed by giving 1–6 points for each additional disease in the pa-

Tab. 1. Obesity status and distribution of comorbid diseases according to FEV_1 value of individuals.

	N=80	FEV_1	
	n (%)	≥ 50 (n=46)	< 50 (n=34)
BMI			
<30 kg/m^2 (non-obese)	52 (65.0)	27 (58.7)	25 (73.5)
≥30 kg/m^2 (obese)	28 (35.0)	19 (41.3)	9 (26.5)
Comorbid disease†			
No	30 (37.5)	18 (39.1)	12 (35.3)
Yes	50 (62.5)	28 (60.9)	22 (64.7)
Heart diseases	26 (32.5)	13 (28.3)	13 (38.2)
Hypertension	26 (32.5)	14 (30.4)	12 (35.3)
Diabetes	18 (22.5)	12 (26.1)	6 (17.6)
Depression	18 (22.5)	10 (21.7)	8 (23.5)
Anemia	12 (15.0)	10 (21.7)	2 (5.9)
Sleep apnea	7 (8.8)	3 (6.5)	4 (11.8)

†Since more than one option can be marked according to these variables, the percentages are calculated over the number "N". Data are presented as number (%)

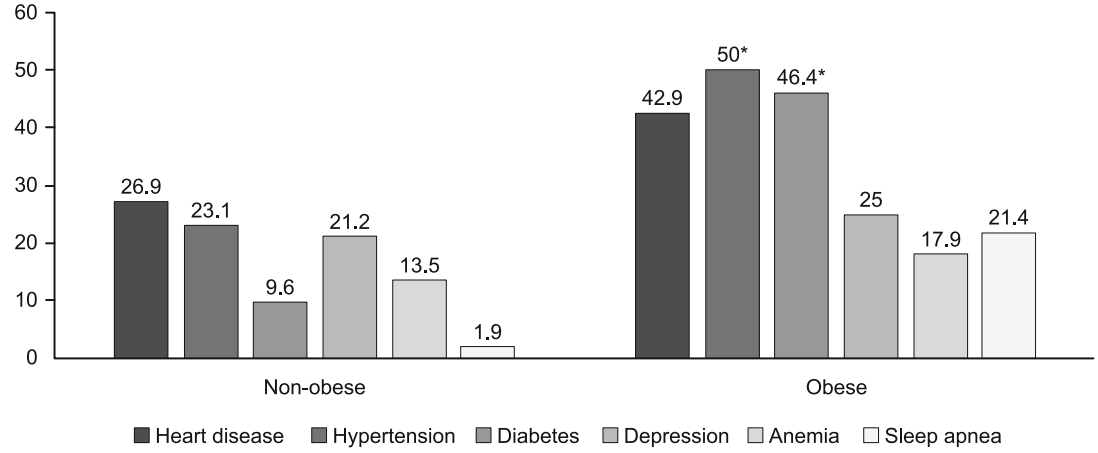

Fig. 1. Comorbid disease incidence rates according to obesity status of individuals (%) * p < 0.05.

tient. Considering that advanced age may also cause comorbidity in the index, the score is increased depending on age. CCI score is calculated by adding one more point for every ten years over the age of 40 to the total score (19). Comorbidities were recorded in the patients with COPD in the study, and the CCI score was obtained.

Pulmonary function test

Spirometric evaluation helps to confirm the diagnosis and monitor the course of the disease. For the diagnosis of COPD, permanent expiratory airflow limitation should be determined in the post-bronchodilator pulmonary function test of the individual at risk. For administration, the individual is first given 400 mcg of salbutamol or 1000 mcg of terbutaline and is left for at least 15–20 minutes. Then, the diagnosis is made if the FEV_1/FVC (forced expiratory volume in the first second/forced vital capacity) ratio measured by spirometry is less than 70 % (10). The most commonly used staging method in the diagnosis of COPD is the GOLD (Global Initiative for Chronic Obstructive Lung Disease) staging system, which classifies patients according to their expected FEV_1% after postbronchodilator (1). The spirometric detection was performed with a ZAN brand spirometry device in 80 patients in the study. FEV_1, FVC, and FEV_1/FVC values of the patients were recorded. The evaluation was made considering the FEV_1 value after the bronchodilator.

mMRC dyspnea scale

The mMRC (modified medical research council) dyspnea scale is an easy-to-use test that evaluates patients' dyspnea. The scale has 5 digits and is a self-rated scale, that is, patients are asked to mark the one that fits them according to their shortness of breath. Scoring on the scale is 0–4; 0 represents the best for dyspnea and 4 the worst for dyspnea (20). The degree of dyspnea provides insight into the risk of future mortality and patients' perception of the disease (20, 21).

Statistical analysis

The "Mann–Whitney U test" (Z-table value) was used in the comparison of two independent groups in data that did not show a normal distribution, and the median was shown with the bottom-up. In correlation tests, "Pearson" and "Spearman" correlation coefficients were used according to normality. $p < 0.05$ was considered statistically significant (22). The SPSS (IBM SPSS Statistics 22.0) package program was used for the statistical analysis of the data. Frequency tables and descriptive statistics were used to interpret the results. Frequency and percentages were utilized for qualitative observations in descriptive analyses, and chi-square analyzes were made and interpreted in comparisons. The "Two-Independent

Tab. 2. Disease markers, anthropometric measurements and blood parameters according to the Charlson comorbidity index score of individuals.

	CCI		p
	< 3 (n=55)	≥ 3 (n=25)	
Exacerbations	0.00 (0.0–8.0)	0.00 (0.0–10.0)	0.893
FEV_1, %	53.64±14.99	54.27±17.18	0.867
FVC, %	70.55±16.18	63.10±19.75	0.079
FEV_1/FVC	59.89±10.73	67.85±11.69	**0.004***
mMRC	1.29±0.79	1.84±0.94	**0.008***
BMİ, kg/m^2	27.27±5.51	30.52±4.42	**0.011***
Waist circumference, cm	101.68±13.80	111.60±10.71	**0.002***
Waist/hip	0.97±0.07	1.02±0.06	**0.006***
Body fat percentage, %	24.05±7.52	27.47±5.99	**0.049***
Neutrophil count, x10^3/uL	5.19 (2.50–10.79)	5.53 (0.50–8.63)	0.674
Lymphocyte count, x10^3/uL	2.39 (1.15–5.40)	2.30 (0.83–5.33)	0.503
Monocyte count, x10^3/uL	0.77 (0.37–1.33)	0.81 (0.30–1.20)	0.807
Leukocyte, x10^3/uL	8.70 (4.96–16.77)	9.33 (3.20–12.77)	0.705

†Since more than one option can be marked according to these variables, the percentages are calculated over the number "N". Data are presented as number (%)

Tab. 3. Neutrophil/lymphocyte ratios of individuals according to disease parameters.

	Neutrophil/lymphocyte ratio	p
FEV_1		
<50	2.52 (0.22–9.38)	**0.013***
≥50	2.06 (1.11–7.34)	
mMRC		
<2	2.06 (1.11–9.38)	**0.015***
≥2	2.59 (0.22–7.34)	
BMI		
<30	2.33 (0.22–9.38)	0.793
≥30	2.12 (1.13–7.34)	
CCI		
<3	2.18 (1.11–9.38)	0.273
≥3	2.61 (0.22–7.34)	

* $p < 0.05$ Data are presented as median (range), mMRC = modified Medical Research Council dyspnea scale, BMI = Body mass index, CCI = Charlson comorbidity index

Sample t" test (t table value) was used in the comparison of two independent groups in the data with normal distribution and is shown with $\bar{X} \pm SS$.

Results

The obesity status and comorbid disease distribution of the individuals in the study are given in Table I. Eighty stable male COPD patients were included in the study. The obesity rate is 41.3 % in individuals with mild/moderate COPD ($FEV_1 \geq 50$) and 26.5 % in individuals with severe COPD ($FEV_1 < 50$). The most common comorbid diseases in the patients were found to be heart diseases (32.5 %) and hypertension (32.5 %). 60.9 % of individuals with mild/moderate COPD and 64.7 % of individuals with severe COPD were diagnosed with a comorbid disease. The distribution of comorbid diseases in obese and non-obese individuals is presented in Figure 1. The incidence of hypertension and diabetes is significantly higher in obese individuals ($p < 0.05$).

Disease markers, anthropometric measurements, and blood parameters according to the CCI score are given in Table 2. BMI, waist circumference, waist/hip ratio, and body fat percentage of individuals with CCI score ≥ 3 were significantly higher than those with CCI score < 3 ($p < 0.05$). NLR values of individuals according to disease parameters are shown in Table 3. NLR was significantly higher in patients with $FEV_1 < 50$ ($p = 0.013$) and mMRC score ≥ 2 ($p = 0.015$). Table 4 shows the correlation table of the variables.

Tab. 4. Correlation table of variables.

	1		2		3		4	
	r	p	r	p	r	p	r	p
1. CCI								
2. NLR	0.145	0.200						
3. BMI	0.231	**0.039***	–0.084	0.457				
4. FEV_1	–0.035	0.757	–0.280	**0.012***	0.170	0.132		
5. mMRC	0.300	**0.007***	0.294	**0.008***	0.102	0.307	–0.337	**0.002***

* $p < 0.05$, CCI = Charlson comorbidity index, NLR = Neutrophil/lymphocyte ratio, BMI = Body mass index, mMRC = modified Medical Research Council dyspnea scale

Discussion

In this study, the researchers aimed to evaluate the relationship between prognostic parameters such as obesity, the Charlson comorbidity index, and neutrophil/lymphocyte ratio and disease severity in COPD. The results revealed an increase in comorbid diseases and CCI in obese patients and an increase in NLR in stable COPD patients with severe airflow obstruction and dyspnea.

Comorbidities

More than two-thirds of COPD patients have one or more comorbidities (9). The comorbid disease has been reported in 54.5 % of male COPD patients (23). Clinically, there is a strong correlation between pulmonary dysfunction and cardiovascular morbidity and mortality. Due to the strong anatomical and functional relationship between the lungs and the heart, a dysfunction affecting one of the organs in the body may also affect other organs (24). Üstünova and Nahcivan found that hypertension (65 %), heart diseases (34 %), and diabetes (25 %) were most common in COPD patients (25). In a study conducted in the USA, it was reported that 65 % of COPD patients had hypertension, and 45 % had cardiovascular disease (26). In another study, cardiovascular disease comorbidity, particularly congestive heart failure, was higher in COPD patients (24.4 %) than those in the control group (13.5 %) (27).

Although there are controversial findings regarding the relationship between impaired lung function and the risk of developing diabetes, it is known that the prevalence of diabetes in COPD patients is 10–14 %. The prevalence of diabetes has been reported to be higher, especially in patients with severe COPD (28, 29). In addition, COPD patients generally prefer to live in isolation due to their physical problems and cannot participate in many social activities (30). Thus, as expected, there was a prevalence of up to 47 % of clinically significant symptoms of depression/anxiety among these patients (31, 32).

In this study, the presence of comorbid diseases in the participants was 62.5 %, and the most common comorbid diseases were cardiovascular diseases, hypertension, diabetes, and depression. Dyspnea also increases in individuals with a high degree of comorbidity. When compared with the literature, it is concluded that comorbidities are common among patients with COPD, and some comorbid diseases are more common, consistent with previous studies. In addition, the number of comorbidities was found to be related to the symptoms of the disease.

The relation between obesity and comorbidity

Various studies have shown that cardiovascular comorbidities, including hypertension, often co-exist with COPD and are associated with increased BMI (33–35). A recent study by Zewari et al (2018) emphasized that obesity is common in patients with COPD and is most common in GOLD I-II stages (mild/moderate COPD) and least in GOLD IV (very severe COPD) (3). In ad-

dition, our study showed that there are different comorbidities in obese and non-obese COPD patients. Cardiovascular and metabolic comorbidities (especially hypertension and diabetes mellitus) are more common in obese COPD patients (3, 36). According to the 2010 data of the Turkish Nutrition and Health Survey (TNHS), the prevalence of obesity among adult men is 20.5 %. In our study, we found the prevalence of obesity to be 35 % among male individuals with COPD. It appears that obesity is more common in men with COPD than in the general population. In terms of the risk of obesity-related chronic disease in males, WHO classifies waist circumference as < 94 cm normal, 94–102 cm risky, and ≥ 102 cm high risk (17). Therefore, in our study, individuals with a CCI ≥ 3 were in the high-risk category of the mean waist circumference, and the incidence of hypertension and diabetes in obese individuals was significantly higher than in non-obese ones. In conclusion, obesity is associated with different clinical outcomes an increased number of comorbidities, and different comorbidity patterns in COPD.

Inflammation

Decreased lung function in COPD patients is associated with increased inflammatory markers, including sputum neutrophils, fibrinogen, and some acute-phase proteins such as C-reactive protein (CRP) (37, 38). In addition, a low-grade inflammation demonstrated by increased blood leukocyte levels, acute phase proteins, and other inflammatory cytokines has also been associated with stable COPD (37). With the formation of inflammation, deterioration in the functional status of patients with COPD is observed over time. This is caused by impaired gas exchange due to symptoms like dyspnea, cough, and fatigue, which are observed in all lung diseases (10).

NLR is considered as a new inflammatory marker in the evaluation of inflammation in COPD patients with its rapid, inexpensive, and easily measurable feature by routine complete blood count analysis (37, 39). In stable COPD patients, however, the use of NLR as a marker has only been evaluated in the last few years (37, 39–41). Furutate et al (2016) examined 141 COPD patients to evaluate the relationship between NLR and clinical parameters in stable patients. While NLR was positively correlated with the BODE (BMI, airflow obstruction, dyspnea, exercise capacity) index and mMRC score, which is a composite marker of the disease, it was inversely correlated with FEV_1 and the 6-minute walk test. A significant correlation was also observed between CRP and NLR (39). Likewise, we found a negative correlation between NLR and FEV_1, and a positive correlation between NLR and mMRC dyspnea scale in our study. We also showed that patients with $FEV_1 < 50$ and mMRC ≥ 2 had a significantly higher NLR. Therefore, it appears that NLR is associated with disease severity and symptoms in individuals with COPD. NLR also increased with increasing disease severity and symptoms in COPD.

The relation between inflammation and comorbidity

The pathogenic mechanisms underlying comorbidities in COPD remain unclear. It has been hypothesized that the transfer of inflammatory mediators from the lung to the systemic circulation contributes to the development of comorbidities in COPD patients (24). It is thought that the chronic inflammatory process has a leading role in the pathogenesis of COPD and may be responsible for the increased comorbidity rate. Inflammation may be effective in the development of cardiovascular diseases, especially among COPD patients, but the exact mechanism is still unclear. In addition, smoking can increase the risk of insulin resistance and diabetes, which are very common in COPD, by creating systemic inflammation in the body (28, 36). However, it should be noted that not only systemic inflammation but also the use of corticosteroids, especially systemic corticosteroids, may contribute to the development of diabetes mellitus in COPD patients (42, 43). There is evidence that systemic inflammation is involved in the pathogenesis of depression (44). Despite these findings in the literature, we could not detect a significant relationship between CCI score and NLR in our study. Although NLR is higher in patients with a high CCI score, the difference is not significant. Likewise, Furutate et al (2016) also evaluated the relationship between NLR and clinical parameters in stable patients and found no significant difference between NLR and CCI (39). However, it should be emphasized here that the CCI scale does not include all comorbid diseases. Therefore, we could not evaluate the link between comorbidities not included in the CCI score and NLR. NLR may also be affected by many factors such as smoking and alcohol consumption, apart from various comorbid diseases such as systemic infections, atherosclerosis, hypertension, chronic kidney disease, and diabetes (45). According to this new concept of "multimorbidity", where multiple diseases coexist with common risk factors such as smoking, immobility, and age in COPD patients, various chronic diseases may have synergistic effects on general health status (46). Therefore, multiple morbid conditions and their risk factors may have interacted with NLR and influenced it in this study. Considering this new concept and the findings of our study, we speculate that not only systemic inflammation but also other factors such as age may cause comorbidities in COPD patients.

Conclusions

Hypertension and diabetes mellitus are the most common comorbidities in obese COPD patients. The increase in comorbidities exacerbates the symptoms of the disease in COPD patients. Therefore, active screening for these comorbidities should be a priority and focus, especially for physicians treating obese COPD patients with high comorbidities, and medical nutrition therapy of obesity should be given importance with the coordination of dietitian. Treatment of the most common comorbidities can improve disease prognosis and reduce mortality. However, how to treat obesity in COPD patients remains a question that needs to be evaluated more comprehensively in the future due to the obesity paradox. At this point, NLR appears to have several advantages for the characterization of COPD as it is a simple, inexpensive, and easily applicable indicator. Since NLR is associated with FEV_1 and mMRC, it can provide valuable information in the clinical assessment of the disease. The benefit of NLR in COPD patients should be elucidated in future studies in clinical settings.

References

1. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J 2019; 53: 1900164.

2. Velasco R, Pirraglia PA, Casserly B, Nici L. Influence of body mass index on changes in disease-specific quality of life of veterans completing pulmonary rehabilitation. J Cardiopulmon Rehab Prevention 2010; 30: 334–339.

3. Zewari S, Hadi L, van den Elshout F, Dekhuijzen R, Heijdra Y, Vos P. Obesity in COPD: comorbidities with practical consequences? COPD: J Chronic Obstructive Pulmonary Dis 2018; 15: 464–471.

4. Hallin R, Gudmundsson G, Ulrik CS, Nieminen MM, Gislason T, Lindberg E et al. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). Respir Med 2007; 101: 1954–1960.

5. Hallin R, Koivisto-Hursti U-K, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). Respir Med 2006; 100: 561–567.

6. Zapatero A, Barba R, Ruiz J, Losa J, Plaza S, Canora J et al. Malnutrition and obesity: influence in mortality and readmissions in chronic obstructive pulmonary disease patients. J Human Nutrit Dietetics 2013; 26: 16–22.

7. Schols AM, Ferreira IM, Franssen FM, Gosker HR, Janssens W, Muscaritoli M et al. Nutritional assessment and therapy in COPD: a European Respiratory Society statement. Eur Respir Soc 2014; 44: 1504–1520.

8. van den Borst B, Gosker HR, Koster A, Yu B, Kritchevsky SB, Liu Y et al. The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. Amer J Clin Nutrit 2012; 96: 516–526.

9. Viegi G, Pistelli F, Sherrill D, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. Eur Respir J 2007; 30: 993–1013.

10. Kocabaş A, Atiş S, Çöplü L, Erdinç E, Ergan B, Gürgün A et al. Kronik obstrüktif akciğer hastaliği (KOAH) koruma, tani ve tedavi raporu 2014. Official J the Turkish Thoracic Society 2014; 15: 1–72.

11. Barnes PJ, Shapiro SD, Pauwels R. Chronic obstructive pulmonary disease: molecular and cellularmechanisms. Eur Respir J 2003; 22: 672–688.

12. Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease–antiprotease imbalance, and inflammation. Internat J Chronic Obstructive Pulmon Dis 2011; 6: 413.

13. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012; 225: 456–460.

14. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Med J 2001; 102: 5–14.

15. Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinellu E, Pirina P et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. Eur Respir Rev 2018; 27: 170113.

16. Gibson RS. Principles of nutritional assessment. Oxford University Press, USA, 2005.

17. World Health Organization (WHO). Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008. 2011.

18. Consultation WE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet (London, England) 2004; 363: 157–163.

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383.

20. Bestall J, Paul E, Garrod R, Garnham R, Jones P, Wedzicha J. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54: 581–586.

21. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. New Engl J Med 2004; 350: 1005–1012.

22. Alpar R. Uygulamali çok değişkenli istatistiksel yöntemlere giriş-I: Bağirgan Yayimevi. 1997.

23. Başyiğit İ, Boyaci H, Argun Bariş S. Kadin ve erkek KOAH'li olgularin karşilaştirilmasi. Solunum Hastaliklari 2010; 21: 41–45.

24. Barnes P, Celli B. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009; 33: 1165–1185.

25. Üstünova E, Nahcivan N. Kronik obstrüktif akciğer hastaliği olan bireylerin kronik hastalik yönetimine ilişkin değerlendirmeleri ve ilişkili faktörler. Florence Nightingale Hemşirelik Dergisi 2015; 23: 11–22.

26. Mapel DW, Dalal AA, Johnson PT, Becker LK, Hunter AG. Application of the new GOLD COPD staging system to a US primary care cohort, with comparison to physician and patient impressions of severity. Internat J Chronic Obstructive Pulmonary Dis 2015; 10: 1477–1486.

27. Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991–1999. J Chronic Obstructive Pulmonary Dis 2005; 2: 35–41.

28. Laghi F, Adiguzel N, Tobin M. Endocrinological derangements in COPD. Eur Respir J 2009; 34: 975–996.

29. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008; 32: 962–969.

30. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly patients with chronic obstructive pulmonary disease. Oxford University Press, 2006.

31. Mikkelsen RL, Middelboe T, Pisinger C, Stage KB. Anxiety and depression in patients with chronic obstructive pulmonary disease (COPD). A review. Nordic J Psychiatry 2004; 58: 65–70.

32. Hill K, Geist R, Goldstein R, Lacasse Y. Anxiety and depression in end-stage COPD. Eur Respir J 2008; 31: 667–677.

33. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med 2015; 3: 631–639.

34. Divo MJ, Cabrera C, Casanova C, Marin JM, Pinto-Plata VM, de-Torres JP et al. Comorbidity distribution, clinical expression and survival in COPD patients with different body mass index. Chronic Obstructive Pulmonary Dis 2014; 1: 229–238.

35. Mihalache A, Fitting J, Nicod L. Chronic obstructive pulmonary disease and its links with cardiovascular risk factors. Rev Med Suisse 2015; 11: 2151–2, 2154–6.

36. Bolton C, Evans M, Ionescu A, Edwards S, Morris R, Dunseath G et al. Insulin resistance and inflammation—a further systemic complication of COPD. J Chronic Obstructive Pulmonary Dis 2007; 4: 121–126.

37. Günay E, Ulaşli SS, Akar O, Ahsen A, Günay S, Koyuncu T et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37: 374–380.

38. Stockley RA. Progression of chronic obstructive pulmonary disease: impact of inflammation, comorbidities and therapeutic intervention. Curr Med Res Opinion 2009; 25: 1235–1245.

39. Furutate R, Ishii T, Motegi T, Hattori K, Kusunoki Y, Gemma A et al. The neutrophil to lymphocyte ratio is related to disease severity and exacerbation in patients with chronic obstructive pulmonary disease. Internal Med 2016; 55: 223–229.

40. Arisoy A, Memiç K, Erçen Diken Ö, Karavelioğlu Y, Demirelli S, Topçu S et al. Evaluation of atrial conduction features in stable chronic obstructive pulmonary disease patients and its relationship with neutrophil to lymphocyte ratio. Acta Med Mediterranea 2015; 31: 343–349.

41. Taylan M, Demir M, Kaya H, Selimoglu Sen H, Abakay O, Carkanat Aİ et al. Alterations of the neutrophil–lymphocyte ratio during the period of stable and acute exacerbation of chronic obstructive pulmonary disease patients. Clin Respir J 2017; 11: 311–317.

42. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society 2008; 5: 549–555.

43. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007; 370: 797–799.

44. Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: comorbidity between depression and neurodegenerative disorders. Progress Neurobiol 2008; 85: 1–74.

45. Balta S, Cakar M, Demirkol S, Arslan Z, Akhan M. Higher neutrophil to lymhocyte ratio in patients with metabolic syndrome. SAGE Publications Sage CA: Los Angeles, CA, 2013.

46. Van Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P et al. Risk factors and comorbidities in the preclinical stages of chronic obstructive pulmonary disease. Amer J Respir Crit Care Med 2014; 189: 30–33.

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