CLINICAL STUDY

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

Elif ADANUR UZUNLAR1, Hilal YILDIRAN2, Nurdan KOKTURK3, Hatice KILIC4, Hatice Canan HASANOGLU4

Karadeniz Technical University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Trabzon, Turkey. elfadanur@hotmail.com

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 (FEV1 ≥ 50) and 26.5 % in those with severe COPD (FEV1 < 50). There was a positive and significant correlation between CCI value and BMI and mMRC dyspnea scale. NLR was significantly higher in patients with FEV1 < 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).

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
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 is not used 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/height², kg/m²) 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/m²) (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-

<table>
<thead>
<tr>
<th>Comorbid disease</th>
<th>BMI</th>
<th>FEV1 ≥ 50</th>
<th>FEV1 &lt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30 kg/m² (non-obese)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (95.0)</td>
<td>2 (5.0)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>No</td>
<td>39 (97.5)</td>
<td>1 (2.5)</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

Tab. 1. Obesity status and distribution of comorbid diseases according to FEV1 value of individuals.

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.

<table>
<thead>
<tr>
<th>Non-obese</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>26.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.6</td>
</tr>
<tr>
<td>Depression</td>
<td>21.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.5</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disease Markers</th>
<th>CCI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations</td>
<td>≤ 3 (n=55)</td>
<td>≥ 3 (n=25)</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>53.6±14.99</td>
<td>54.27±17.18</td>
</tr>
<tr>
<td>FVC, %</td>
<td>70.55±16.18</td>
<td>63.10±19.75</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>59.89±10.73</td>
<td>67.85±11.69</td>
</tr>
<tr>
<td>mMRC</td>
<td>1.29±0.79</td>
<td>1.84±0.94</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.27±5.51</td>
<td>30.52±4.42</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>101.68±13.80</td>
<td>111.60±10.71</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.97±0.07</td>
<td>1.02±0.06</td>
</tr>
<tr>
<td>Body fat percentage, %</td>
<td>24.05±5.52</td>
<td>27.47±5.99</td>
</tr>
<tr>
<td>Neutrophil count, x10³/uL</td>
<td>5.19 (2.50–10.79)</td>
<td>5.53 (0.50–8.63)</td>
</tr>
<tr>
<td>Lymphocyte count, x10³/uL</td>
<td>2.39 (1.15–5.40)</td>
<td>2.30 (0.83–5.33)</td>
</tr>
<tr>
<td>Monocyte count, x10³/uL</td>
<td>0.77 (0.37–1.33)</td>
<td>0.81 (0.30–1.20)</td>
</tr>
<tr>
<td>Leukocyte, x10³/uL</td>
<td>8.70 (4.96–16.77)</td>
<td>9.33 (3.20–12.77)</td>
</tr>
</tbody>
</table>

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
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 X ± SS.

**Results**

The obesity status and comorbid disease distribution of the individuals in the study are given in Table 1. Eighty stable male COPD patients were included in the study. The obesity rate is 41.3 % in individuals with mild/moderate COPD (FEV₁ ≥ 50) and 26.5 % in individuals with severe COPD (FEV₁ < 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 FEV₁ < 50 (*p* = 0.013) and mMRC score ≥ 2 (*p* = 0.015). Table 4 shows the correlation table of the variables.

**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 Nahićivan 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 prevalence 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.
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 FEV₁ 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 FEV₁ and a positive correlation between NLR and mMRC dyspnea scale in our study. We also showed that patients with FEV₁ < 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 circula-

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 FEV₁ 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


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