# AIM OF THE WORK

The first aim of the work is to investigate the role of plasma leptin as an inflammatory cytokine in COPD by comparing its level in patients with stable COPD, patients with COPD exacerbations and a control healthy group.

Second is to correlate circulating levels of leptin to the inflammatory marker CRP, the severity of the disease according to GOLD criteria and the BODE index as a prognostic indicator in patients with COPD.

# PATIENTS

The study was performed on 2 groups of subjects: the study group (A) and the control group (B). All subjects were males in order to increase homogeneity of the study population. All patients were recruited from Chest Department in Alexandria Main University Hospital during the period from January 2014 to July 2014. Subjects involved in the study were divided as follows:

**Group A**: The study group (A) formed of forty patients with COPD was subdivided into two subgroups:

- **Subgroup (A1)**: Included twenty patients with **COPD exacerbation.**
- **Subgroup (A2)**: Included twenty patients with **Stable COPD.**

All patients fulfilled the following criteria:

**Inclusion Criteria:**

1. A clinical diagnosis of COPD according to GOLD and spirometry results with a post bronchodilator fixed ratio of FEV1/FVC <70% predicted confirming the presence of persistent airflow limitation.
2. **For subgroup (A1): COPD exacerbation group**: Clinical manifestations of acute exacerbation defined by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication. [1]
3. **For Subgroup (A2) : Stable COPD group**: Clinically stable condition with absence, for at least 8 weeks, of clinical signs or symptoms of acute exacerbation, with no requirements for increases in treatment.

**Exclusion Criteria:**

1. Presence of renal disorders.
2. Presence of hepatic disorders.
3. Presence of malignancy.
4. Presence of blood coagulation disorders.
5. Presence of lipodystrophy.
6. Presence of collagen vascular disease.
7. Presence of metabolic syndrome.
8. Presence of heart failure.
9. Body mass index more than or equal to 30 $kg/m^2$.
10. Presence of any inflammatory conditions other than COPD.

**Group B**: The control group formed of twenty five healthy, non-smokers, age and sex matched volunteers.

# METHODS

## I.For the study group (A)

Each patient was subjected to the following:

**1-A comprehensive medical history focusing on:**

- History of smoking and exposure to other risk factors of COPD.
- Cardinal symptoms of COPD including chronic and progressive dyspnea, cough and sputum production that can be variable from day to day and any additional features like fatigue, weight loss, anorexia, depression and anxiety. [1]
- Evidence of presence or absence of current exacerbation manifested by worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication, including baseline dyspnea, cough and sputum production. [1] Patients with absence, for at least 8 weeks, of clinical signs or symptoms of acute exacerbation, with no requirements for increases in treatment will be considered clinically stable.
- History of other mimicking conditions e.g. bronchial asthma, bronchiectasis and TB.
- History of other non-respiratory symptoms.
- Past medical and family history.
- History of having any of the previously mentioned exclusion criteria.

**2-Full clinical examination:** including general examination, vital signs and local chest examination.

**3-Plain X-ray chest PA view.**

**4-Full routine laboratory assessment** including:

- Complete blood count.
- Renal function tests.
- Liver function tests.
- Serum electrolytes.
- Lipid profile.
- Fasting and postprandial blood sugar.

**5-Electrocardiography.**

**6-Spirometry:** The measurements were obtained before and 15 minutes after inhaling 400 µg of salbutamol. An increase in FEV1% and/or FVC ≥12% of control and ≥200 ml constitutes a positive bronchodilator response. [311]

**7- Staging of the patients according to GOLD spirometric criteria** [1] (table 2).

**8-Arterial blood gases analysis.**

**Table 2 : Classification of severity of airflow limitation according to GOLD criteria** [1]

| Classification of severity of airflow limitation in COPD based on postbronchodilator FEV1% | | |
|---|---|---|
| **In patients with FEV1/FVC <0.70** | | |
| **GOLD 1** | Mild | FEV1 ≥ 80% predicted |
| **GOLD 2** | Moderate | 50%≤ FEV < 80% predicted |
| **GOLD 3** | Severe | 30%≤ FEV1< 50% predicted |
| **GOLD 4** | Very severe | FEV1 <30% predicted |

**9-BODE index scoring**: Points from each variable are added according to the threshold value measured for each one. The value ranges from (0) to a maximum of (10) [153] (table 3). BODE index variables consist of:

a) Body mass index: Weight and height were measured to compute the body mass index using the Quetelet's index; weight (kg) /[height(m)]$^2$. [312] A body mass index more than or equal to 30 kg/m$^2$ will be excluded (table 4).

b) Degree of airflow obstruction: Assessed by spirometry before and 15 minutes after inhaling 400 µg of salbutamol. [311]

c) Dyspnea assessment by the modified Medical Research Council (MRC) scale: A five-point scale based on degrees of various physical activities that precipitate dyspnea with a score ranging from (0-4) (table 5). [150]

d) Exercise capacity assessment by the 6-minute walk distance test (6MWT): The test was conducted following the recommendations of ATS by measuring the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. Two tests were performed in a 33-meter-long corridor by the same investigator with the use of standard phrases of encouragement at the end of each minute. The greater distance reached in the two tests was used for analysis. [313]

**Table 3: Calculation of the BODE index** [153]

| BODE index | | | | |
|---|---|---|---|---|
| | Points on BODE index | | | |
| **Variable** | **0** | **1** | **2** | **3** |
| **FEV1 %** | ≥65 | 50-64 | 36-49 | ≤35 |
| **6MWT** | ≥350 | 250-349 | 150-249 | ≤149 |
| **mMRC** | 0-1 | 2 | 3 | 4 |
| **BMI** | >21 | ≤21 | | |

**Table 4: Classification of BMI according to WHO** [314]

| Classification | BMI (Kg/m$^2$) |
|---|---|
| **Underweight** | <18.50 |
| **Normal range** | 18.50-24.99 |
| **Overweight** | ≥25.00 |
| **Obese** | ≥30.00 |
| Obese class I | 30.00-34.99 |
| Obese class II | 35.00-39.99 |
| Obese class III | ≥40.00 |

**Table 5: The modified Medical Research Council scale for assessing the severity of breathlessness** [1]

| Grade | Description of Breathlessness |
|---|---|
| **0** | I only get breathless with strenuous exercise. |
| **1** | I get short of breath when hurrying on level ground or walking up a slight hill. |
| **2** | On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace. |
| **3** | I stop for breath after walking about 100 yards or after a few minutes on level ground. |
| **4** | I am too breathless to leave the house or I am breathless when dressing. |

**10-Staging of the patients according to the combined COPD assessment:** Using mMRC score to assess the impact of dyspnea and assessment of exacerbation risk based on the individual patient's history of exacerbations with two or more exacerbations per year indicating high risk. Assessment pointing to the highest risk was used in case of discrepancy between criteria (figure 3) (table 6).

**11-CRP level measurement using immune-turbidimitry technique.**

**12-Fasting plasma Leptin measurement**: Using enzyme immunoassay for the measurement by DRG Leptin (Sandwich) ELISA kits. (DRG International, Inc., USA). Normal values are shown in (table 7).

**Table 6: Categorization of the patients according to the combined COPD assessment classification** [1]

| Patient category | Characteristics | Spirometric classification | Exacerbations per year | mMRC | CAT |
|---|---|---|---|---|---|
| **A** | Low risk, less symptoms | GOLD 1-2 | 1 | 0-1 | <10 |
| **B** | Low risk, more symptoms | GOLD 1-2 | 1 | 2 | 10 |
| **C** | High risk, less symptoms | GOLD 3-4 | 2 | 0-1 | <10 |
| **D** | High risk, more symptoms | GOLD 3-4 | 2 | 2 | 10 |

## II.For the control group (B)

The following was performed for all subjects:

**1-A comprehensive medical history** focusing on:

- History of smoking and exposure to other risk factors of COPD.
- Cardinal symptoms of COPD including chronic and progressive dyspnea, cough and sputum production that can be variable from day to day and any additional features like fatigue, weight loss, anorexia, depression and anxiety. [1]
- History of other mimicking conditions e.g. bronchial asthma, bronchiectasis and TB.
- Past medical and family history.
- History of having any of the previously mentioned exclusion criteria.

**2-CRP level measurement using immune-turbidimitry technique.**

**3- Fasting plasma Leptin measurement:** Using enzyme immunoassay for the measurement by DRG Leptin (Sandwich) ELISA kits. (DRG International, Inc., USA)

**Table 7: Normal values of leptin**

| Population | ng/ml |
|---|---|
| **Males** | 3.84 +/- 1.79 |
| **Females** | 7.36 +/- 3.73 |

# RESULTS

Forty patients with COPD and twenty five healthy control subjects were enrolled in this study, during the period from January 2014 to July 2014. Subjects involved in the study were divided as follows:

**1-Group A**: The study group (A) formed of forty patients with COPD and had been subdivided into two subgroups:

- **Subgroup (1)**: Twenty patients with **COPD exacerbation.**
- **Subgroup (2)**: Twenty patients with S**table COPD.**

**2-Group B:** The control group formed of twenty five healthy age and sex matched volunteers.

## Characteristics of the study population:

The different characteristics of the study population are shown in (table 8).

### Gender

All the enrolled subjects were males in order to increase homogeneity of the study population and eliminate the gender related differences in leptin measurements.

### Age

The mean ± SD of age for subgroup A1 (COPD exacerbation) was (58.15 ± 8.37 years), for the subgroup A2 (Stable COPD) was (57.65 ± 8.04 years) and for group B (controls) was (54.92 ± 6.84 years). There was no statistically significant difference between the three groups (p=0.317).

### Smoking Status

For both COPD patients subgroups, 6 patients were ex-smokers (30%) and 14 patients were current smokers (70%). Smoking index mean ± SD for subgroup A1 was (37.57 ± 8.0 pack-years) and for subgroup A2 was (39.0 ± 6.55 pack-years). No passive or non-smokers were present in the study group A. No statistically significant difference detected between the two groups. The control group B subjects were non-smokers.

### Exacerbations per year

The mean ± SD of exacerbations annual rate was (2.5 ± 1.0 exacerbations/year) for subgroup A1, and (2.15 ± 0.933 exacerbations /year) for subgroup A2 with no statistical significant difference between the two groups.

## Body mass index

The mean ± SD of BMI for subgroup A1 was (22.46 ± 3.26 kg/m$^2$), for sub group A2 was (20.71 ± 4.22 kg/m$^2$) and that for group B was (22.27 ± 3.01 kg/m$^2$). There was no statistically significant difference between the three groups.

**Table 8: Characteristics of the study population**

| **Patients' characteristics** | **Subgroup A1 COPD Exacerbation (n=20)** | | **Subgroup A2 Stable COPD (n=20)** | | **Group B Controls (n=25)** | **Test of Significance** | **p** |
|---|---|---|---|---|---|---|---|
| **Age** (years) | 58.15 ± 8.37 | | 57.65 ± 8.04 | | 54.92 ± 6.84 | F=1.169 | 0.317 |
| **BMI** (Kg/m$^2$) | 22.46 ± 3.26 | | 20.71 ± 4.22 | | 22.27 ± 3.01 | F=1.553 | 0.220 |
| **Exacerbations/year** | 2.5 ± 1.0 | | 2.15 ± 0.933 | | - | Z=1.226 | 0.260 |
| **Smoking index** (pack-years) | 37.57 ± 8.0 | | 39.0 ± 6.55 | | - | t = 0.517 | 0.610 |
| **Smoking status** | **No.** | **%** | **No.** | **%** | Non smokers | $\chi^2$ = 0.0 | 1.00 |
| Ex-smoker | 6 | 30.00 | 6 | 30.00 | | | |
| Smoker | 14 | 70.00 | 14 | 70.00 | | | |

Data are expressed in mean ± SD.
F: F test (ANOVA); t: Student t-test; Z: Z for Mann Whitney test; $\chi^2$: Chi square test
p: p value for comparing between the two studied groups

## BMI comparison in the stable COPD subgroup:

Within the subgroup A2 (stable COPD), BMI was compared in relation to the different GOLD stages and in relation to the combined COPD assessment groups too (table 9). The comparison showed a statistically significant difference of the BMI in relation to different stages of the disease, with (F=11.209, p=0.001) for GOLD stages and (F=3.770, p=0.044) for the combined COPD assessment groups (figures 6, 7).

**Table 9: Comparison of BMI in the different groups of the stable COPD patients**

| | N | BMI (Kg/m$^2$) Mean ± SD | F | p |
|---|---|---|---|---|
| **GOLD stage** | | | | |
| **II** | 3 | 27.80 ± 1.66 | 11.209* | 0.001* |
| **III** | 6 | 20.77 ± 3.22 | | |
| **IV** | 11 | 18.75 ± 2.99 | | |
| **Combined COPD assessment classification** | | | | |
| **B** | 3 | 25.47 ± 3.77 | 3.770* | 0.044* |
| **C** | 3 | 22.47 ± 5.48 | | |
| **D** | 14 | 19.31 ± 3.36 | | |

F: F test (ANOVA)
*: Statistically significant at $p \leq 0.05$

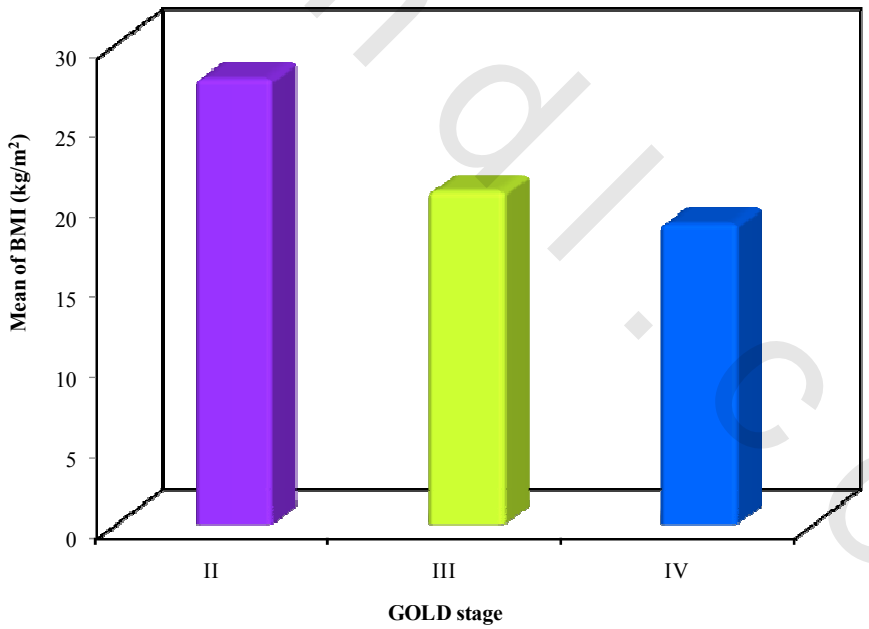


**Figure 6:** Relation between BMI and GOLD stages in the stable COPD subgroup

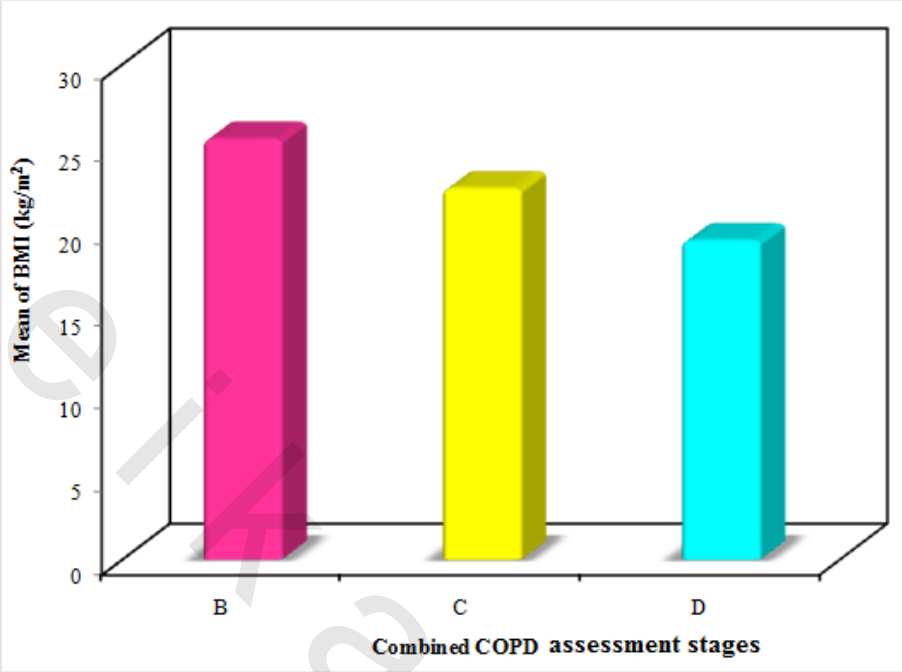


**Figure 7:** Relation between BMI and combined COPD assessment groups in the stable COPD subgroup

## Spirometric measurements of the studied patients:

### FEV1/FVC ratio

As regard subgroup A1, the mean ± SD of FEV1/FVC % was (46.20 ± 11.10) and for subgroup A2 was (40.96 ±11.82). There was no statistically significant difference between the two groups (table 10).

### FEV1% predicted

The mean ± SD of predicted FEV1 % for subgroup A1 was (39.42 ± 18.67) and that for subgroup A2 was (37.26 ±16.19). Also no statistically significant difference was detected (table 10).

**Table 10: Comparison between the patients' groups according to FEV1/FVC and FEV1%**

| | Subgroup A1 COPD Exacerbation (n=20) | Subgroup A2 Stable COPD (n=20) | t | p |
|---|---|---|---|---|
| **FEV1/FVC** Mean ± SD. | 46.20 ± 11.10 | 40.96 ±11.82 | 1.445 | 0.157 |
| **FEV1%** Mean ± SD. | 39.42 ± 18.67 | 37.26 ±16.19 | 0.391 | 0.698 |

t: Student t-test

## Functional status of the studied patients:

### Modified medical research council dyspnea scale (mMRC)

As for subgroup A1, the mean score ± SD of mMRC was (2.60 ± 0.59) and that for subgroup A2 was (2.35 ± 0.74), with no statically significant difference between the two subgroups (table 11).

### Six-minute walk test (6MWT)

The mean ± SD of the measured distance by 6MWT for subgroup A1 was (211.80 ± 75.45 meters) while that for subgroup A2 was (248.25 ± 66.88 meters) (table 11). There was a statically significant difference between the two subgroups (p=0.049) (figure 8).

**Table 11: Comparison between the two patients' subgroups according to mMRC**

| | Subgroup A1 COPD Exacerbation (n=20) | Subgroup A2 Stable COPD (n=20) | Test of sig. | p |
|---|---|---|---|---|
| **mMRC** Mean ± SD. | 2.60 ± 0.59 | 2.35 ± 0.74 | t = 1.170 | 0.249 |
| **6MWT (meters)** Mean ± SD. | 211.80 ± 75.45 | 248.25 ± 66.88 | Z = 1.965* | 0.049* |

p: p value for comparing between the two studied groups
Z: Z for Mann Whitney test; t: Student t-test; *: Statistically significant at p ≤ 0.05

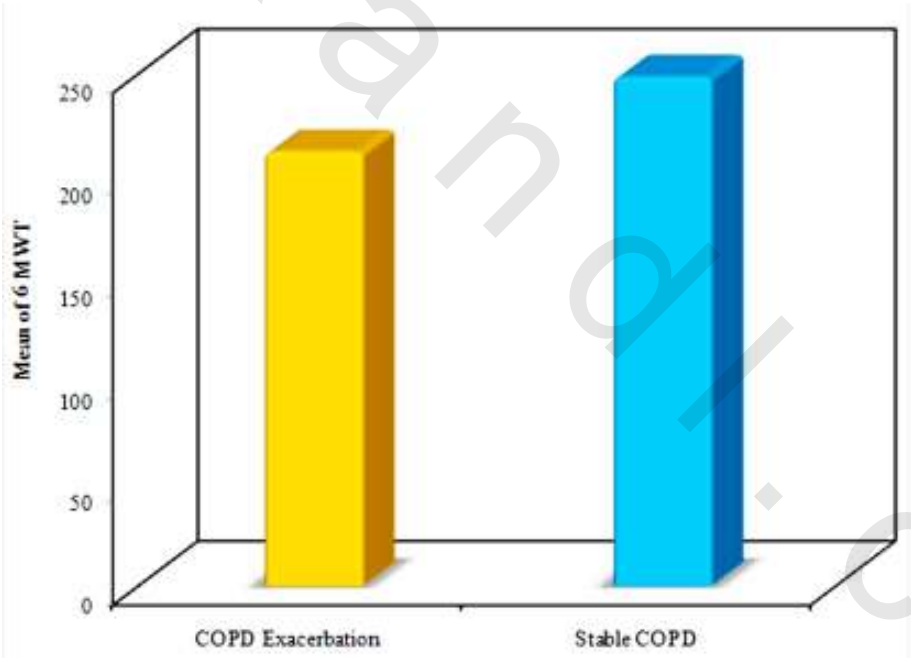


**Figure 8:** Comparison between COPD exacerbation and stable subgroups according to 6MWT

## Severity assessment of the studied patients:

### GOLD staging:

As for subgroup A1 (COPD exacerbation), one patient was GOLD stage I (5.0%), 5 patients were GOLD stage II (25.0%), 7 patients were GOLD stage III (35.0%) and 7 patients were GOLD stage IV (35.0%).

As for subgroup A2 (Stable COPD), 3 patients were GOLD stage II (15.0%), 6 patients were GOLD stage III (30.0%) and 11 patients were GOLD stage IV (55.0%). There was no statistically significant difference between the two subgroups (table 12).

### The combined COPD assessment classification:

Regarding subgroup A1 (COPD exacerbation), 2 patients were stage B (10.0%), 3 patients were stage C (15.0%) and 15 patients were group D (75.0%). For subgroup A2 (Stable COPD), 3 patients were stage B (15.0%), 3 patients were group C (15.0%) and 14 patients were group D (70.0%). No statistically significant difference was detected between the two groups (table 12).

### Percentage of severe cases as shown by GOLD stages and the combined COPD assessment classification:

The comparison of the percentages of severe cases as assessed by the combined COPD assessment groups and the GOLD stages based on FEV1% within COPD exacerbation subgroup revealed a difference between percentages of severe cases within COPD exacerbation subgroup that showed 7 patients with GOLD stage IV (35.0% of the patients), and from the combined COPD assessment view, it was 75.0% of patients (15 patients were group D with high risk and more symptoms) (figure 9).

**Table 12: Comparison between the two studied groups according to GOLD stage and Combined COPD assessment classification**

| | Subgroup A1 COPD Exacerbation (n=20) | | Subgroup A2 Stable COPD (n=20) | | Test of sig. | p |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **GOLD stage** | | | | | | |
| I | 1 | 5.0 | - | - | Z=1.423 | 0.155 |
| II | 5 | 25.0 | 3 | 15.0 | | |
| III | 7 | 35.0 | 6 | 30.0 | | |
| IV | 7 | 35.0 | 11 | 55.0 | | |
| **Combined COPD assessment classification** | | | | | $\chi^2$=0.386 | 1.000 |
| B | 2 | 10.0 | 3 | 15.0 | | |
| C | 3 | 15.0 | 3 | 15.0 | | |
| D | 15 | 75.0 | 14 | 70.0 | | |

Z: Z for Mann Whitney test; $\chi^2$: value for Chi square test

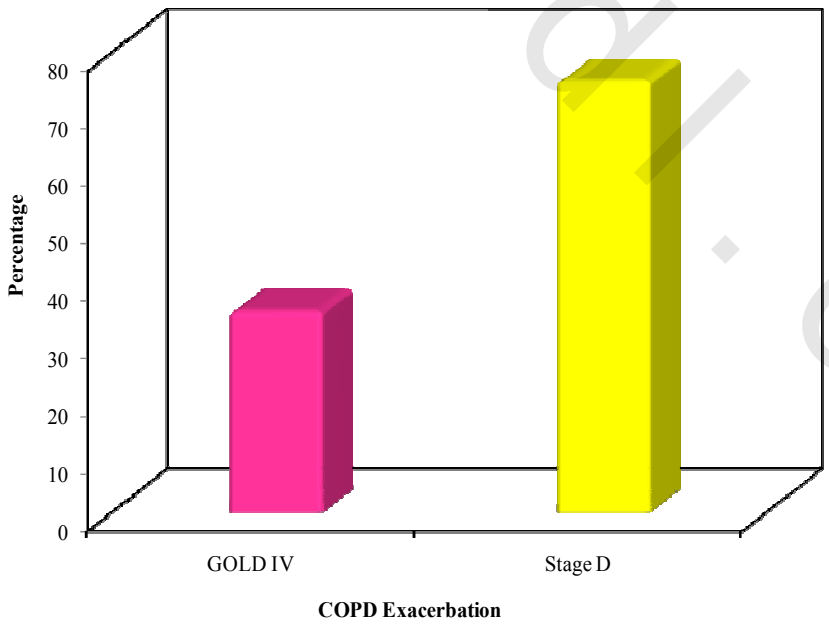


**Figure 9:** Percentage of the very severe cases as shown by GOLD stages and the combined COPD assessment in COPD exacerbation subgroup

## Scoring of BODE index:

Scoring of the BODE index showed no statistically significant difference between the two studied subgroups. The mean ± SD for subgroup A1 was (5.95 ± 2.16) and for subgroup A2 was (5.75 ± 2.09) (table 13).

**Table 13: Comparison between the two studied groups according to BODE score**

| | **Subgroup A1 COPD Exacerbation (n=20)** | **Subgroup A2 Stable COPD (n=20)** | **t** | **p** |
|---|---|---|---|---|
| **BODE score** Mean ± SD. | 5.95 ± 2.16 | 5.75 ± 2.09 | 0.297 | 0.768 |

t: Student t-test

## CRP levels in the studied groups:

The mean ± SD of CRP level for subgroup A1 was (37.66 ± 42.24 mg/l), while that for subgroup A2 was (12.41 ± 13.91 mg/dl).There was a statistically significant difference between the two subgroups (p=0.007). In group B (control subjects), the mean ± SD of CRP level was (2.47 ± 1.63 mg/l). There was a statistically significant difference between group B (controls) and subgroup A1 (COPD exacerbation) and also subgroup A2 (Stable COPD) with p=0.001 for both.

The difference of CRP levels between the three studied groups was statistically significant with ${}^{KW}\chi^2$= 15.065 at p=0.001(table 14) (figure 10).

**Table 14: Comparison between the three studied groups according to CRP**

| | Subgroup A1 COPD Exacerbation (n=20) | Subgroup A2 Stable COPD (n=20) | Control (n=25) | $^{KW}\chi^2$ | p |
|---|---|---|---|---|---|
| **CRP (mg/l)** Mean ± SD. | 37.66 ± 42.24 | 12.41 ± 13.91 | 2.47 ± 1.63 | 15.065* | 0.001* |
| $p_1$ | | 0.007* | 0.001* | | |
| $p_2$ | | 0.003* | | | |

$^{KW}\chi^2$: Kruskal Wallis test
$p_1$: p value for Mann Whitney test for comparing between COPD exacerbation with each other group
$p_2$: p value for Mann Whitney test for comparing between stable COPD and control
*: Statistically significant at $p \leq 0.05$

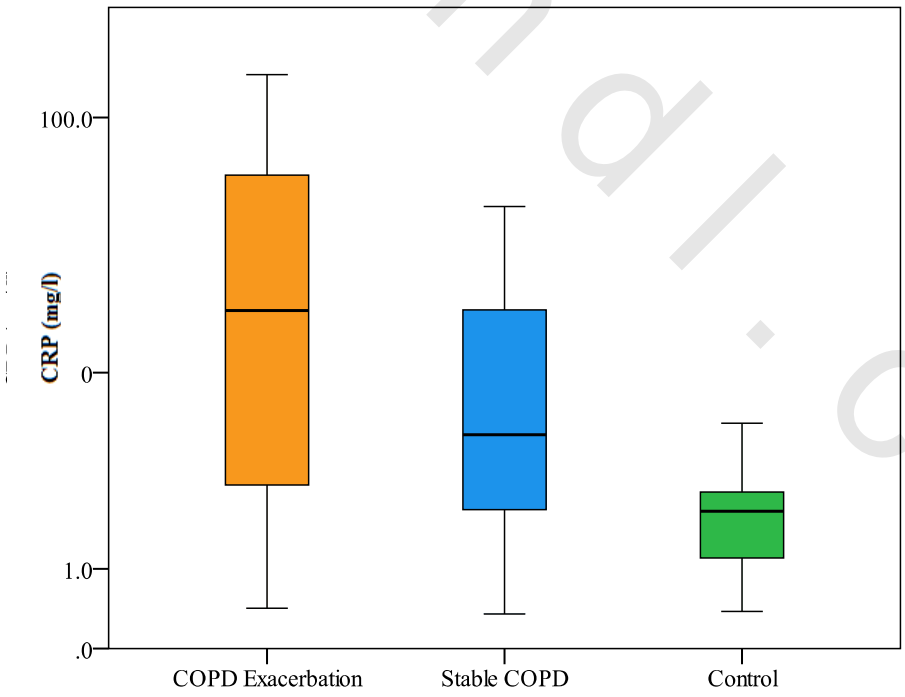


**Figure 10:** Comparison between the three studied groups according to CRP

## Leptin levels in the studied groups:

The mean of leptin level ± SD for subgroup A1 (COPD exacerbation) was (38.25 ± 26.87 ng/ml) while that for subgroup A2 (stable patients) was (9.25 ± 6.10 ng/ml). There was a statistically significant difference between the two subgroups (p=0.001). As for group B (controls), the mean ± SD of leptin was (5.3 ± 3.05 ng/ml). There was a statistically significant difference between group B (controls) and subgroup A1 (COPD exacerbation) (p<0.001). Also there was a statistically significant difference between group B and subgroup A2 (stable patients) (p=0.025).

The comparison between the three studied groups showed a statistically significant difference of the leptin level, with $^{KW}\chi^2$=28.899 at p<0.001(table 15) (figure 11).

**Table 15: Comparison between the three studied groups according to leptin**

| | **Subgroup A1 COPD Exacerbation (n=20)** | **Subgroup A2 Stable COPD (n=20)** | **Control group B (n=25)** | **$^{KW}\chi^2$** | **p** |
|---|---|---|---|---|---|
| **Leptin** Mean ± SD. | 38.25 ± 26.87 | 9.25 ± 6.10 | 5.3 ± 3.05 | 28.899* | <0.001* |
| **$p_1$** | | <0.001* | <0.001* | | |
| **$p_2$** | | 0.025* | | | |

$^{KW}\chi^2$: Kruskal Wallis test
$p_1$: p value for Mann Whitney test for comparing between COPD exacerbation with each other group
$p_2$: p value for Mann Whitney test for comparing between stable COPD and control
*: Statistically significant at $p \leq 0.05$

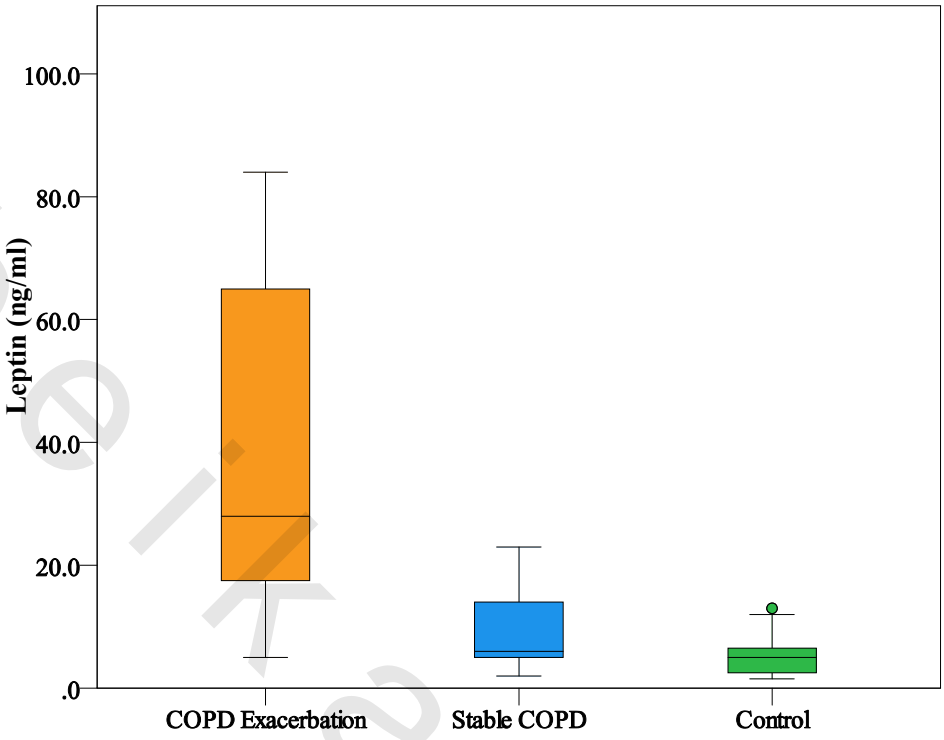


**Figure 11: Comparison between the three studied groups according to leptin**

## Correlation analysis of the different studied parameters

Correlations of BMI in patients with stable COPD:

The BMI measurements have been studied for correlations with different parameters in the stable COPD subgroup (table 16). Results showed the following:

- BMI was negatively correlated with severity assessment by GOLD stages based on FEV1% predicted (r=-0.605, p=0.004) (figure 12)
- BMI was negatively correlated with scores of mMRC dyspnea scales (r=-0.476, p=0.033) (figure 13).
- Other variables including FEV1%, FEV1/FVC and 6MWT showed no significant correlations with BMI.

**Table 16: Correlations of BMI in the stable COPD subgroup**

| BMI (Kg/m$^2$) | Subgroup A2 Stable COPD | |
|---|---|---|
| | $r_s$ | p |
| **FEV1 %** | 0.419 | 0.065 |
| **FEV1/FVC** | 0.355 | 0.1235 |
| **GOLD stage** | -0.605* | 0.004 |
| **6MWT** | 0.004 | 0.984 |
| **mMRC** | -0.476* | 0.033 |

$r_s$: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

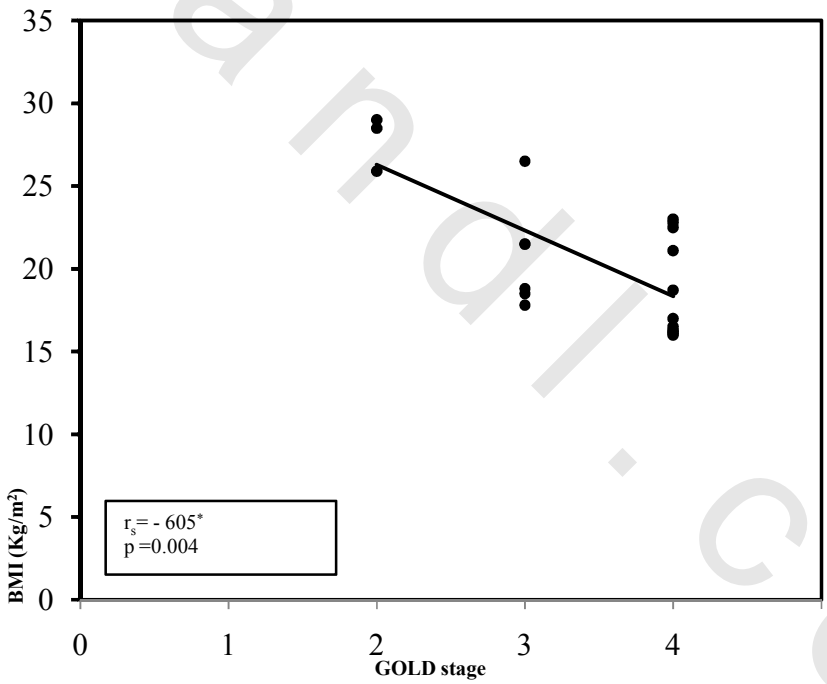


**Figure 12:** Correlation between BMI and GOLD staging in stable COPD subgroup

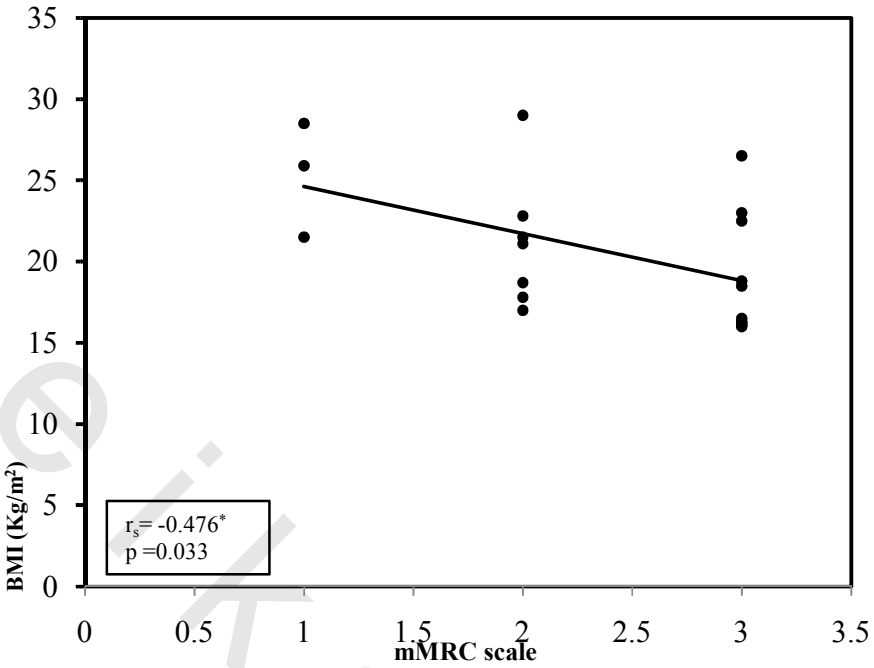


**Figure 13:** Correlation between mMRC scores and BMI in stable COPD subgroup

## Correlations of mMRC scores in the patients' groups:

The scores of mMRC dyspnea scale have been studied for correlations with different functional parameters; results are shown in (table 17). Results showed the following:

**-For subgroup A1 (COPD exacerbation):**

- Scores of mMRC dyspnea scale showed a significant negative correlation with predicted FEV1% (r =-0.729, p=0.002) (figure 14) and also with FEV1/FVC% (r=-0.625, p=0.003) (figure 15).
- Scores of mMRC dyspnea scale showed a significant positive correlation with severity assessment by GOLD staging with r= 0.802 at p<0.001 (figure 16).
- Scores of mMRC dyspnea scale showed a significant negative correlation with the distance measured by the six-minute walk test with r=-0.509 at p=0.021(figure 17).

**-For subgroup A2 (Stable COPD):**

- Scores of mMRC dyspnea scale showed a significant negative correlation with predicted FEV1/FVC% with r=-0.459 at p=0.041 (figure 18).
- Scores of mMRC dyspnea scale showed a significant positive correlation with severity assessment by GOLD staging with r= 0.497 at p<0.025 (figure 19).

**Table 17: Correlation between mMRC scores and other functional parameters in each group**

| mMRC | Subgroup A1 COPD Exacerbation | | Subgroup A2 Stable COPD | |
|---|---|---|---|---|
| | $r_s$ | p | $r_s$ | p |
| **FEV1 %** | -0.729* | 0.002 | -0.4229 | 0.0632 |
| **FEV1/FVC** | -0.625* | 0.0031 | -0.459* | 0.04167 |
| **GOLD stage** | 0.802* | <0.001 | 0.497 * | 0.0255 |
| **6MWT** | -0.509* | 0.0218 | -0.0314 | 0.8954 |

$r_s$: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

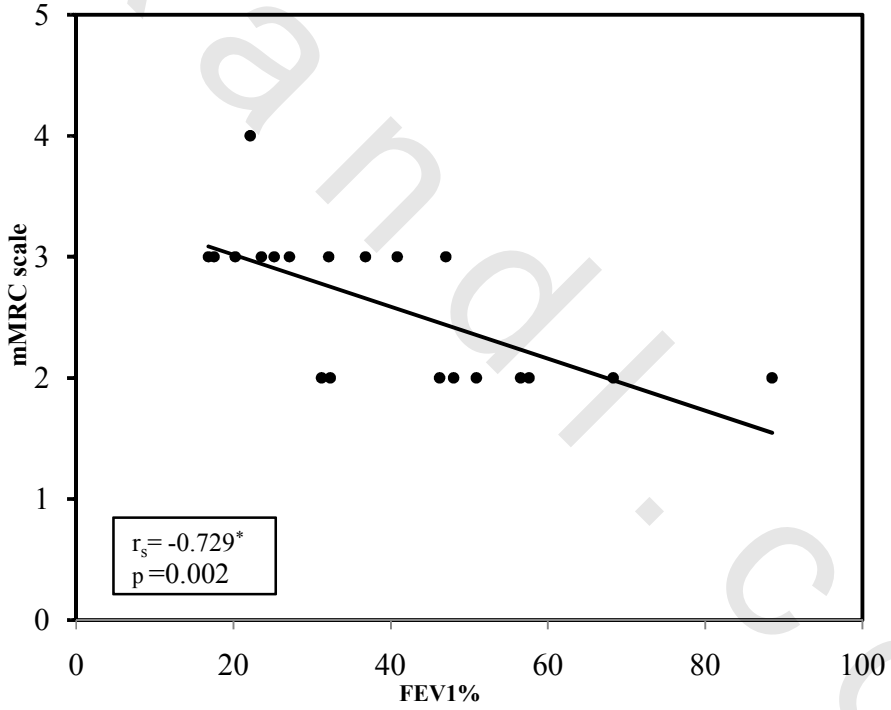


**Figure 14:** Correlation between mMRC score and FEV1% in COPD exacerbation subgroup

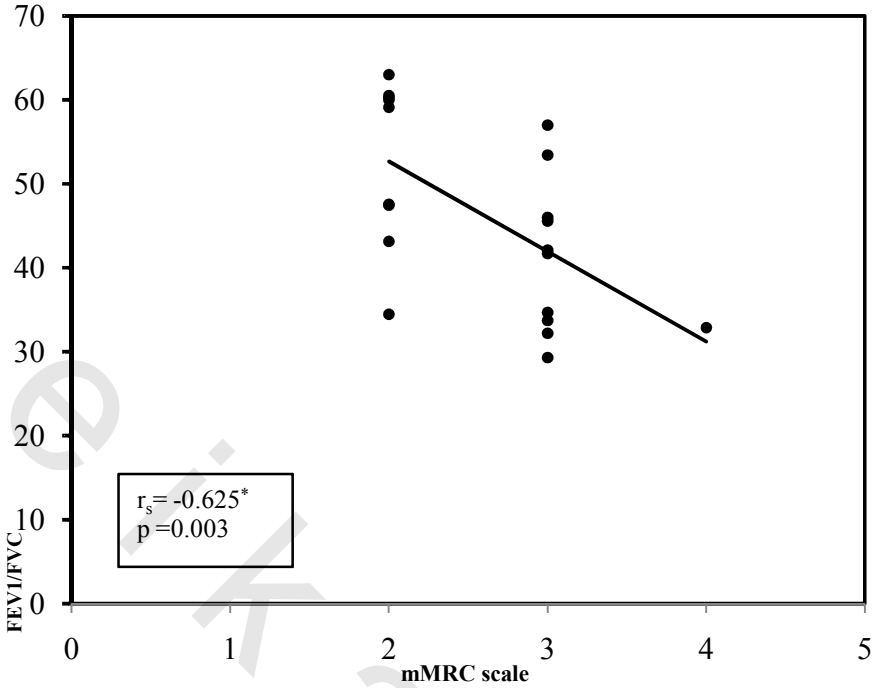


**Figure 15:** Correlation between mMRC score and FEV1/FVC in COPD exacerbation subgroup

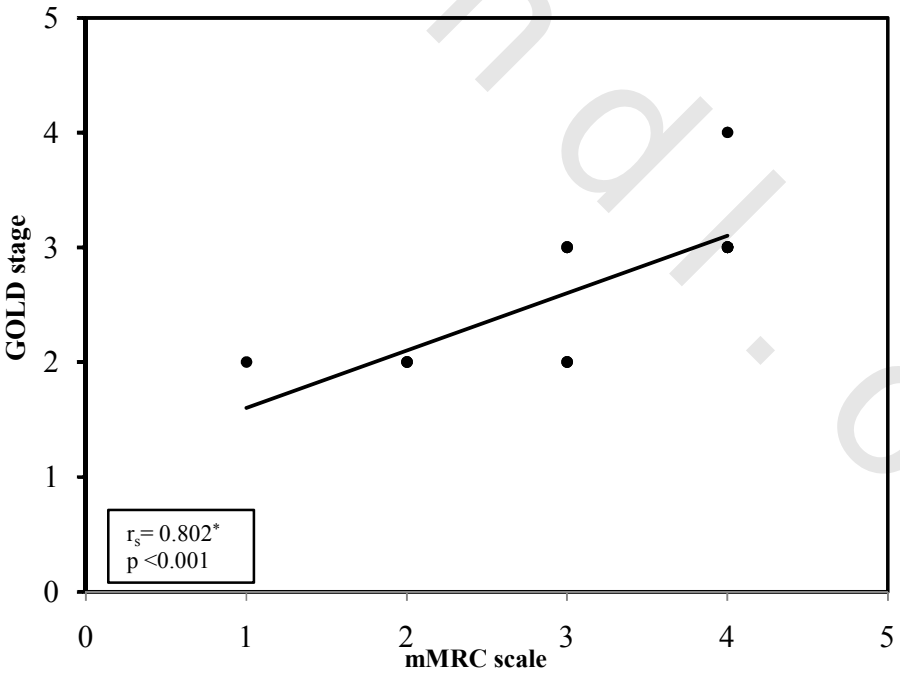


**Figure 16:** Correlation between mMRC score and GOLD stages in COPD exacerbation subgroup

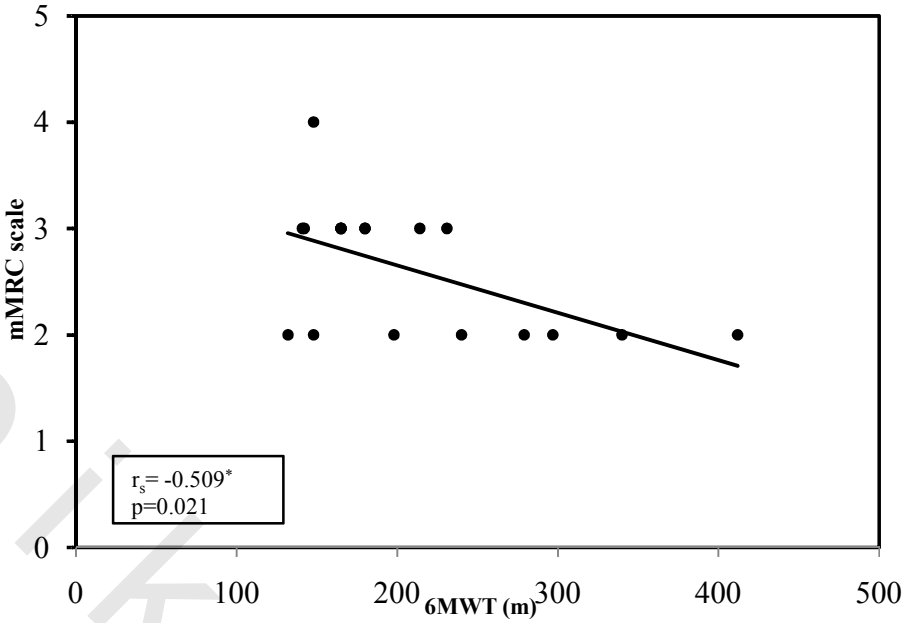


**Figure 17:** Correlation between mMRC score and 6MWT in COPD exacerbation subgroup

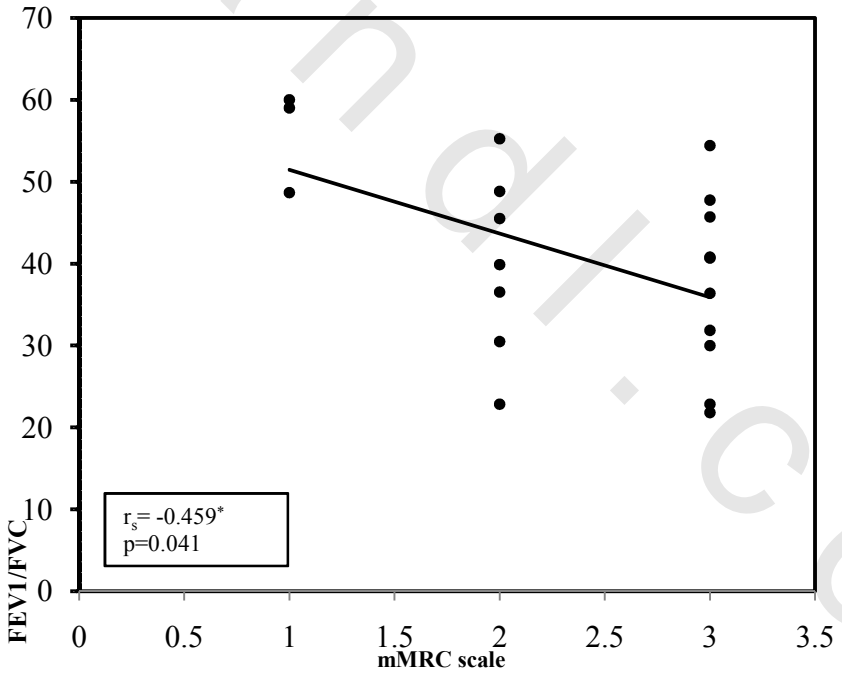


**Figure 18:** Correlation between mMRC score and EFV1/FVC% in stable COPD subgroup

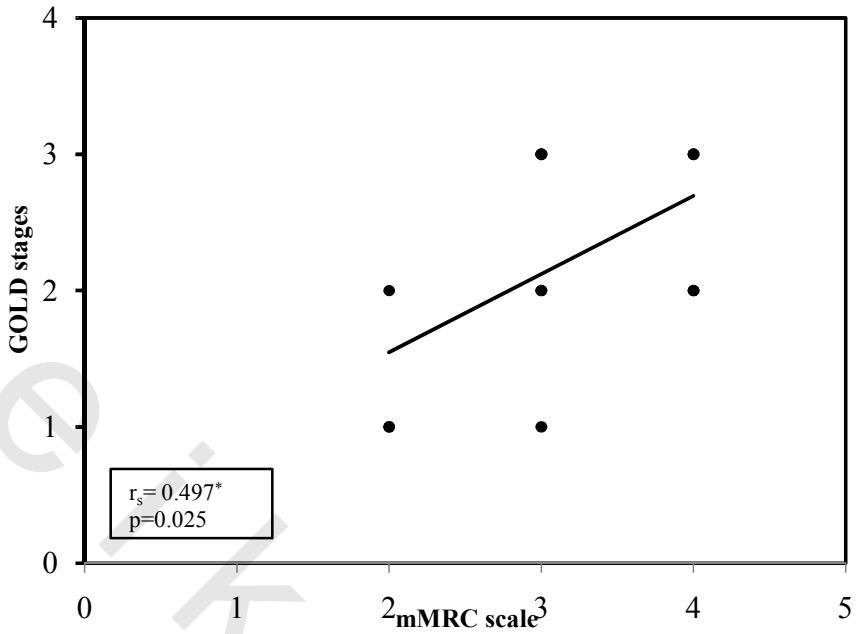


**Figure 19:** Correlation between mMRC score and GOLD stages in stable COPD subgroup

## Correlations of 6MWT results in the patients' groups:

6MWT results have been studied for correlations with different functional parameters in the patients' groups, results are shown in (table 18). Results showed the following:

- The distance measured by 6MWT was positively correlated with FEV1% in COPD exacerbation subgroup (r=0.559, p=0.0103) (figure 20) as well as in stable COPD subgroup (r=0.558, p=0.0105) (figure 21).
- In COPD exacerbation subgroup, 6MWT results were negatively correlated with both severity assessment by GOLD staging (r=-0.474, p=0.034) (figure 22) and with scores of mMRC dyspnea scale (r=-0.509, p=0.021) (figure 17).

**Table 18: Correlation between 6MWT measurement and other functional parameters in each group**

| 6MWT(meters) | Subgroup A1 COPD Exacerbation | | Subgroup A2 Stable COPD | |
|---|---|---|---|---|
| | $r_s$ | p | $r_s$ | p |
| **FEV1 %** | 0.559* | 0.0103 | 0.558* | 0.0105 |
| **FEV1/FVC** | 0.339 | 0.142 | 0.3285 | 0.157 |
| **GOLD stage** | -0.474* | 0.034 | -0.405 | 0.076 |
| **mMRC** | -0.509* | 0.021 | -0.0314 | 0.895 |
| **Combined COPD assessment** | -0.377 | 0.100 | -0.088 | 0.711 |

$r_s$: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

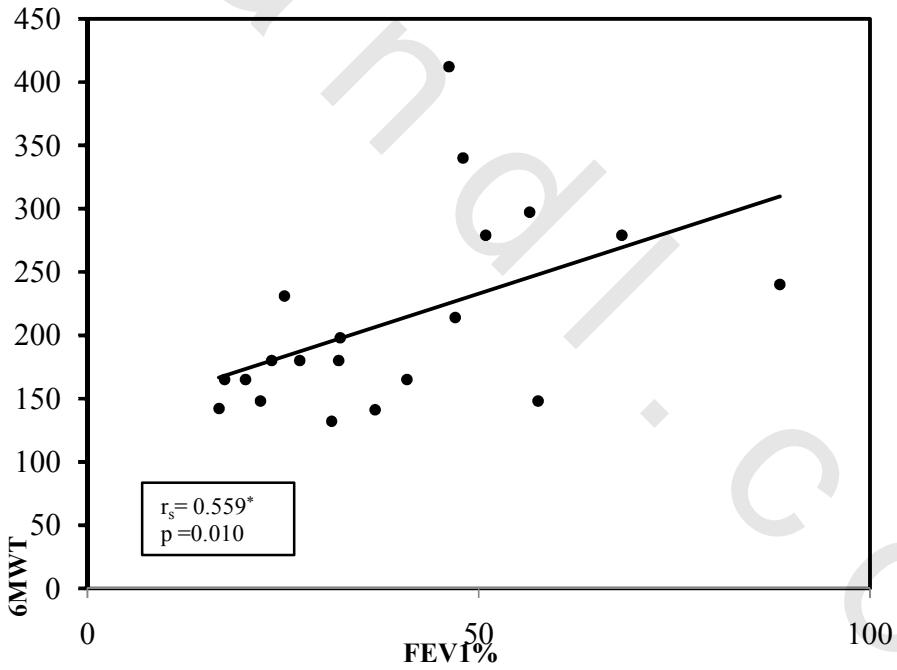


**Figure 20:** Correlation between 6MWT and FEV1% in COPD execration subgroup

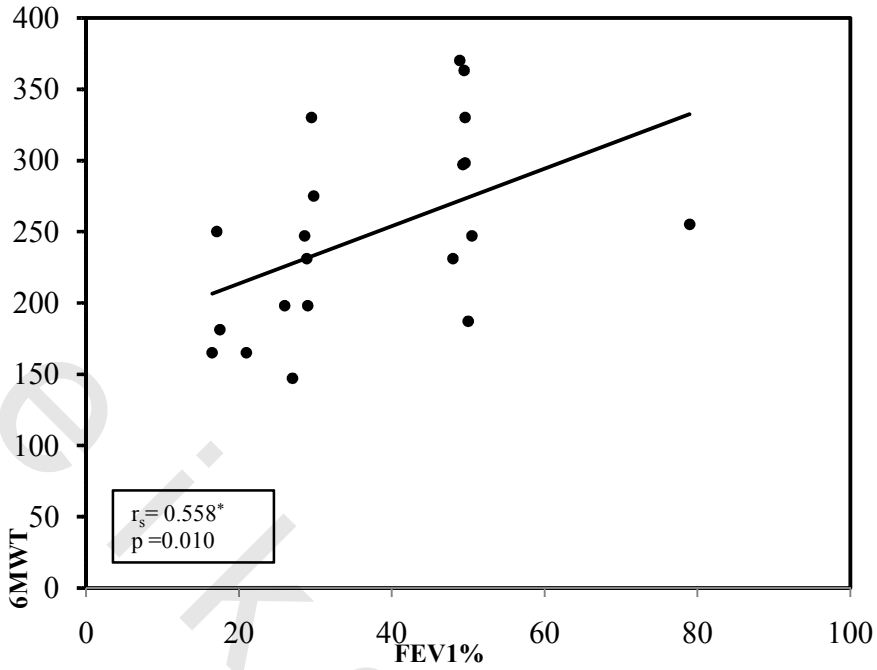


**Figure 21:** Correlation between 6MWT and FEV1% in stable COPD subgroup

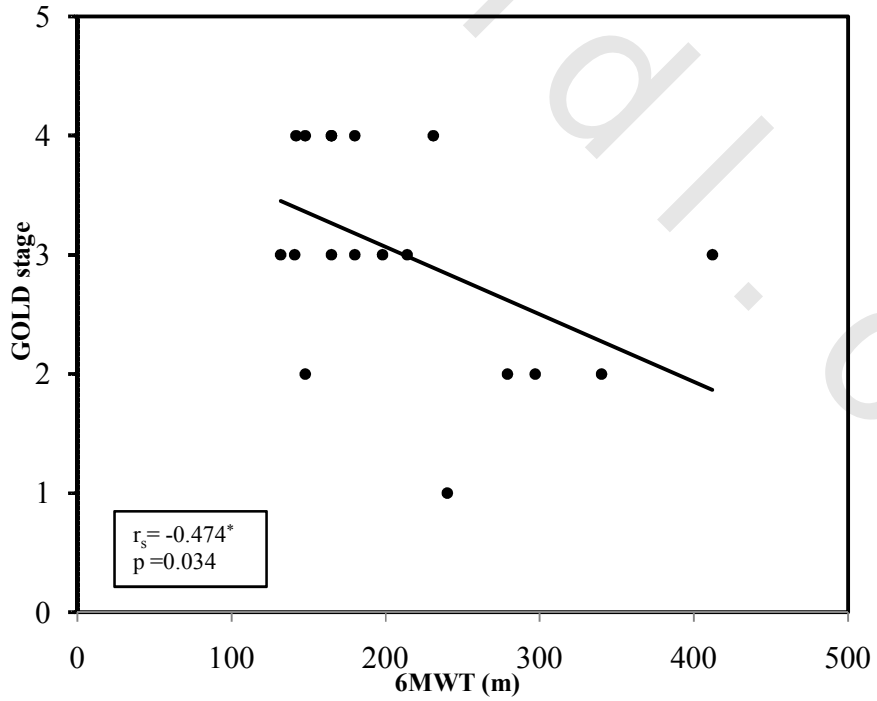


**Figure 22:** Correlation between 6MWT and GOLD stages in COPD exacerbation subgroup

## Correlations of BODE score in the patients' groups:

BODE score had been correlated with different studied parameters in the patients' groups, results are shown in (table 19). Correlation analysis showed the following:

**For subgroup A1 (exacerbation subgroup):**

- BODE score was positively correlated with GOLD staging (r=0.884, p<0.001) (figure 23) and with combined COPD assessment groups (r=0.680, p=0.001) (figure 24).
- BODE score showed also a positive correlation with both CRP levels with r=0.499 at p=0.025(figure 25) and with Leptin level with r=0.834 at p<0.001(figure 26).
- BODE score was negatively correlated with FEV1/FVC ratio (r=-0.620, p=0.004) (figure 27).

**For subgroup A2 (stable subgroup):**

- BODE score showed a positive correlation with GOLD staging (r=0.837, p<0.001) (figure 28) and with combined COPD assessment groups (r=0.733, p<0.001) (figure 29).
- BODE score was negatively correlated with FEV1/FVC ratio (r=-0.624, p=0.003) (figure 30).
- In contrast to the exacerbation group, BODE score was negatively correlated with leptin level in the COPD stable subgroup (r=-0.527, p=0.017) (figure 31).

**Table 19: Correlations between BODE score and different studied parameters in the study group A**

| BODE score | Subgroup A1 COPD Exacerbation | | Subgroup A2 Stable COPD | |
|---|---|---|---|---|
| | $r_s$ | p | $r_s$ | p |
| **FEV1/ FVC** | -0.620* | 0.004 | -0.624* | 0.003 |
| **GOLD stage** | 0.884* | <0.001 | 0.837* | <0.001 |
| **Combined COPD assessment** | 0.680* | 0.001 | 0.733* | <0.001 |
| **CRP(mg/l)** | 0.499* | 0.025 | 0.047 | 0.843 |
| **Leptin (ng/ml)** | 0.834* | <0.001 | -0.527* | 0.017 |

$r_s$: Spearman coefficient ; *: Statistically significant at $p \leq 0.05$

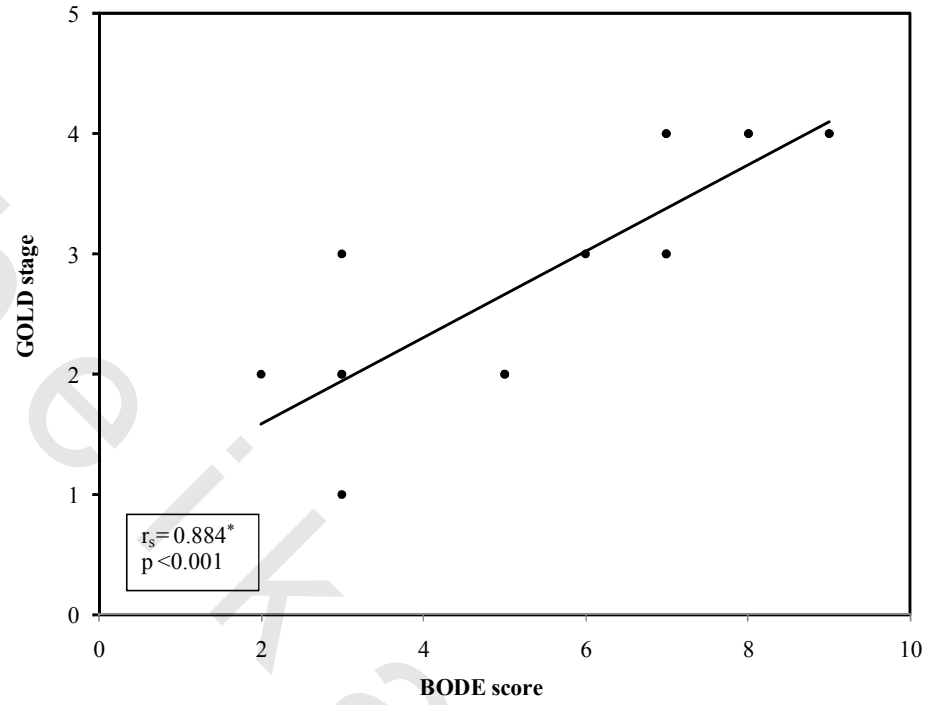


**Figure 23**: Correlation between BODE score and GOLD stage in COPD exacerbation subgroup

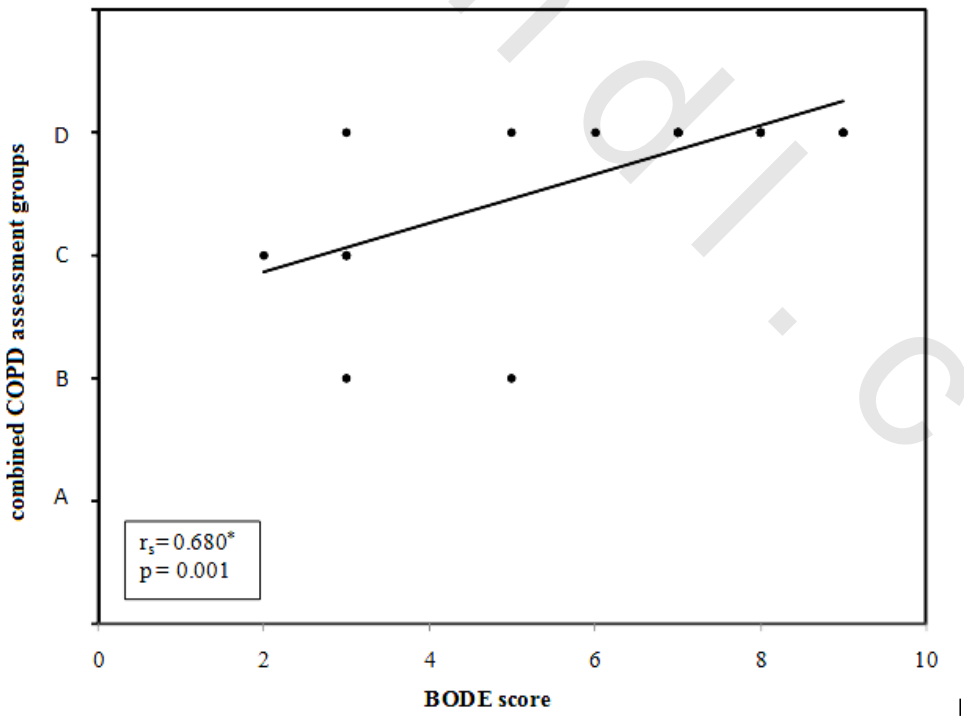


**Figure 24**: Correlation between BODE score and combined COPD assessment groups in COPD exacerbation subgroup

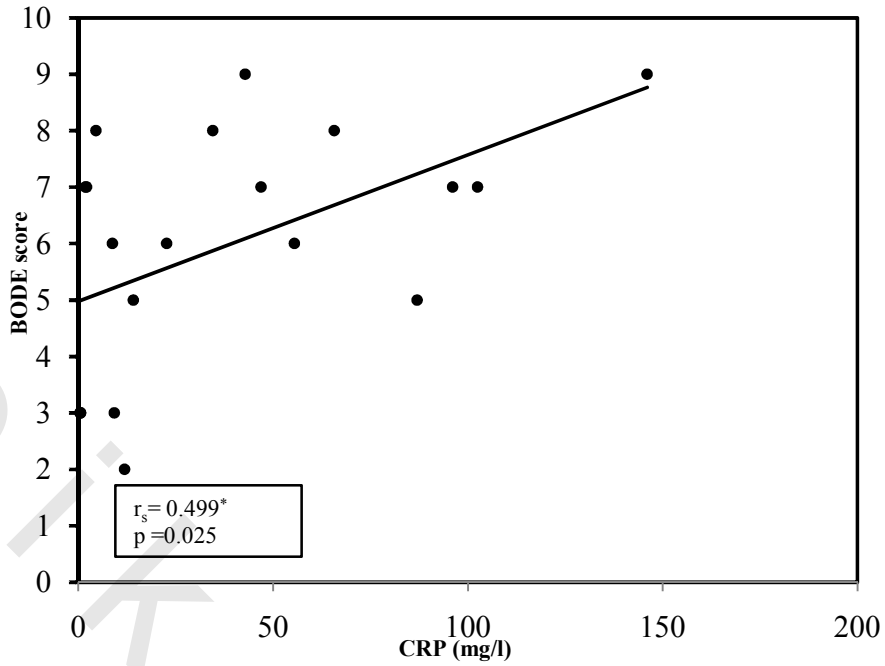


**Figure 25**: Correlation between CRP with BODE score in COPD exacerbation subgroup

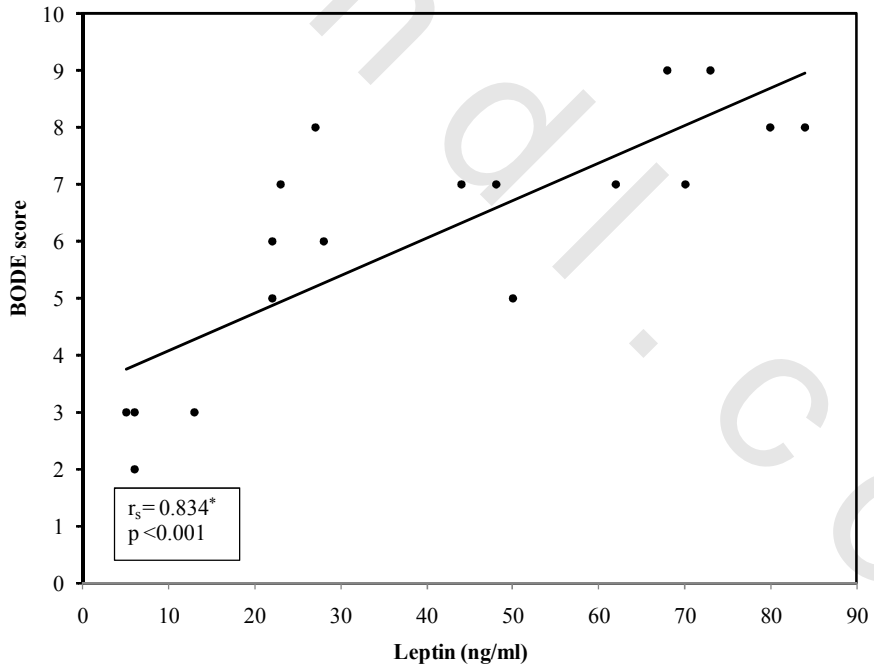


**Figure 26**: Correlation between leptin and BODE score in COPD exacerbation subgroup

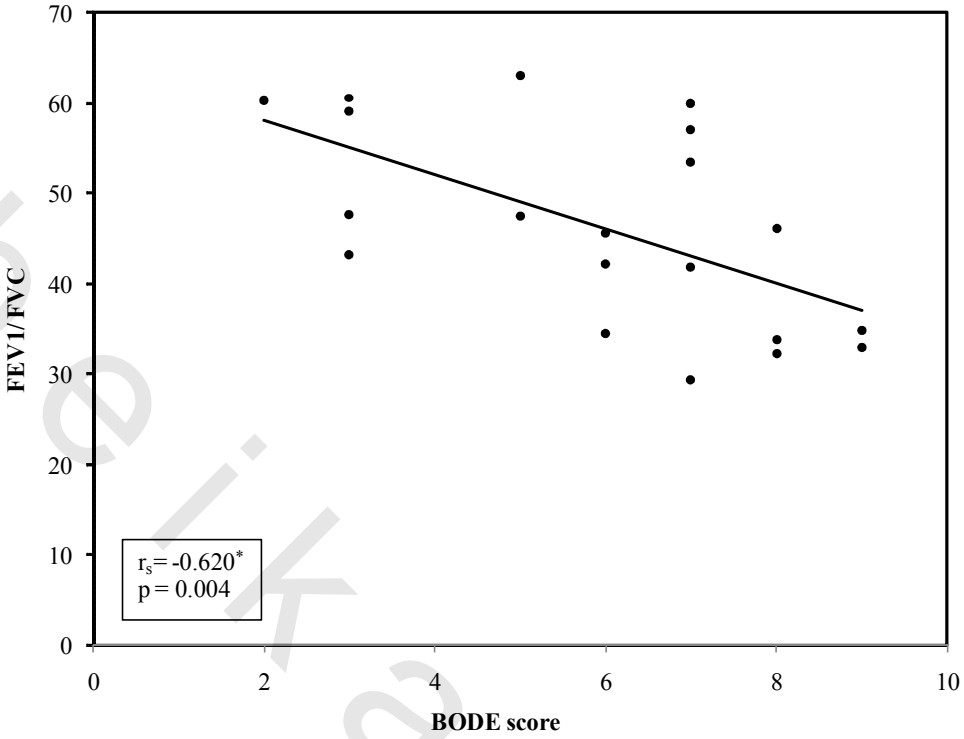


**Figure 27**: Correlation between BODE score and FEV1/ FVC ratio in COPD exacerbation subgroup

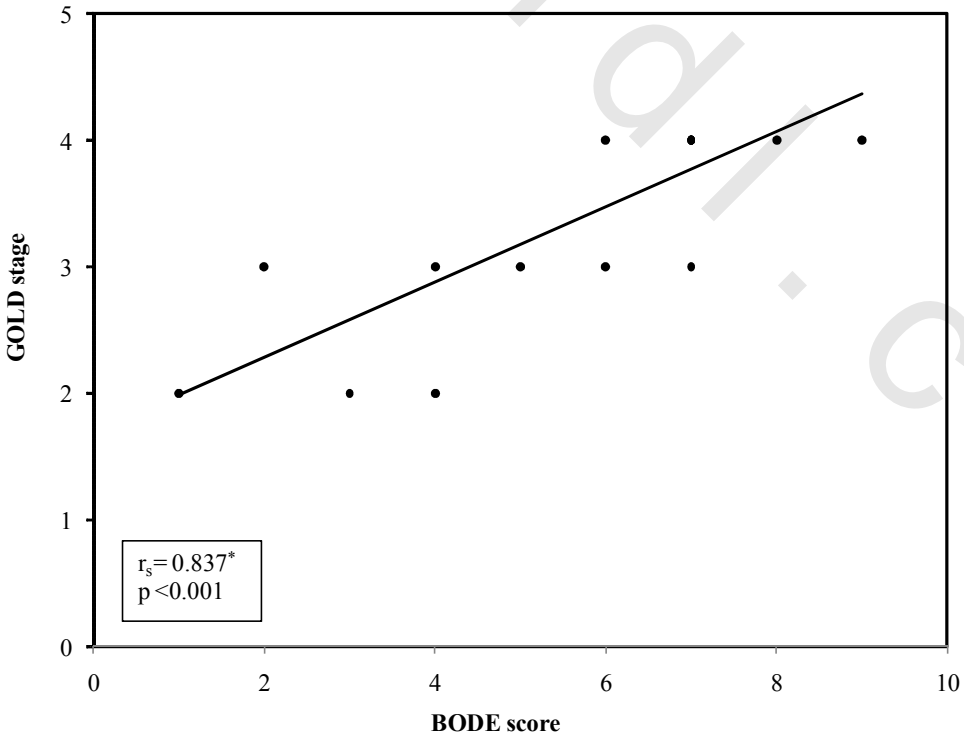


**Figure 28**: Correlation between BODE score and GOLD stages in stable COPD subgroup

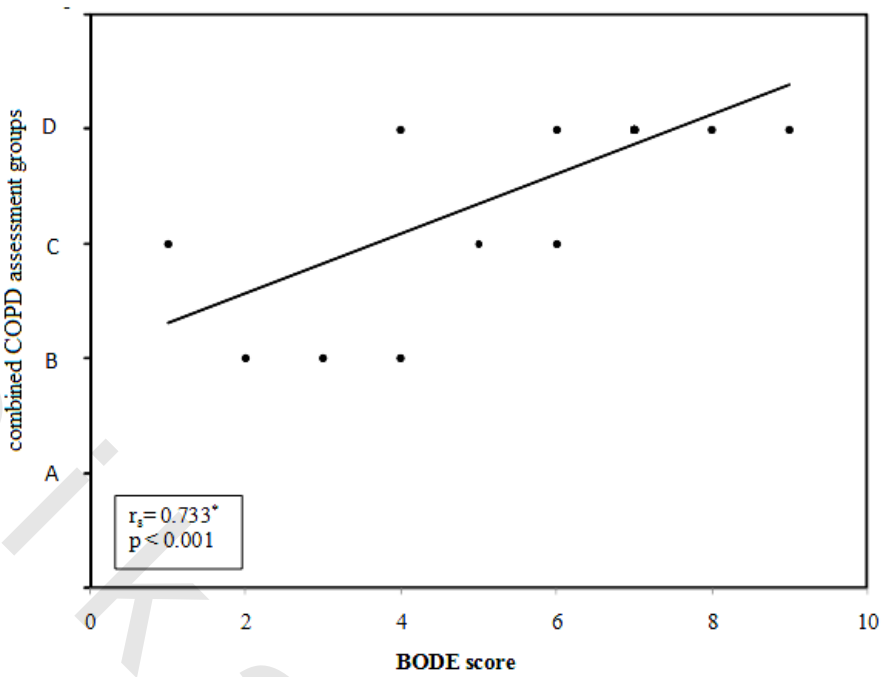


**Figure 29**: Correlation between BODE score and combined COPD assessment in stable COPD subgroup

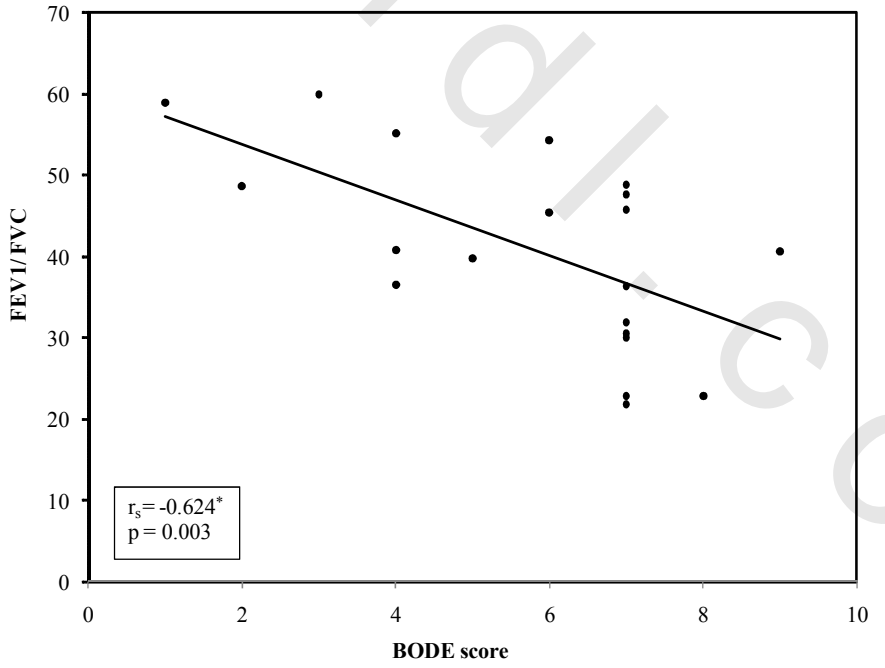


**Figure 30**: Correlation between BODE score and FEV1/ FVC ratio in stable COPD subgroup

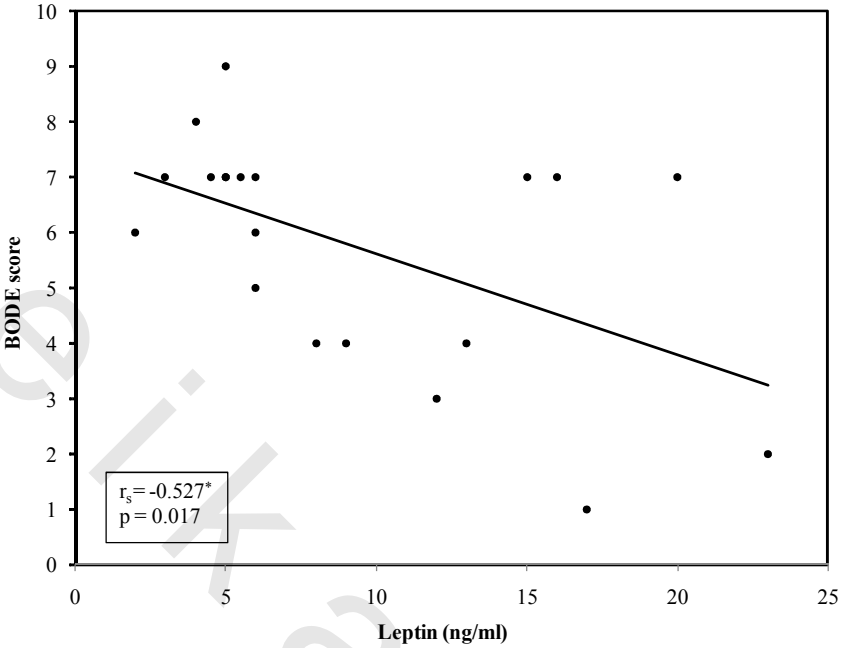


**Figure 31**: Correlation between leptin and BODE score in stable COPD subgroup

## Correlations of CRP in the patients' groups:

CRP levels had been studied for correlations with different studied parameters within the studied patients' groups; results are shown in (table 20). Results showed the following:

**For subgroup A1 (COPD exacerbation):**

- CRP level showed a positive correlation with leptin level with r=0.605 at p=0.005(figure 32).
- CRP level showed a positive correlation with BODE score with r=0.449 at p=0.025 (figure 25).
- By contrast, there were negative correlations between CRP levels and both FEV1% (r=-0.469, p=0.037) (figure 33) and 6MWT (r=-0.561, p=0.010) (figure 34).

**For subgroup A2 (stable COPD):**

- CRP level showed a positive correlation with leptin level (r=0.447, p=0.048) (figure 35).
- CRP level showed a negative correlation with 6MWT (r=-0.454, p=0.045) (figure 36).

**Table 20: Correlation between CRP and different studied parameters in patients' groups**

| CRP (mg/l) | Subgroup A1 COPD Exacerbation | | Subgroup A2 Stable COPD | |
|---|---|---|---|---|
| | $r_s$ | p | $r_s$ | p |
| **Leptin (ng/ml)** | 0.605* | 0.005 | 0.447* | 0.048 |
| **Smoking index** | 0.512 | 0.061 | 0.408 | 0.147 |
| **Exacerbations/y** | -0.146 | 0.540 | -0.205 | 0.385 |
| **FEV1/ FVC** | -0.286 | 0.222 | -0.260 | 0.268 |
| **FEV1%** | -0.469* | 0.037 | -0.394 | 0.086 |
| **GOLD stage** | 0.361 | 0.118 | 0.016 | 0.947 |
| **6MWT** | -0.561* | 0.010 | -0.454* | 0.045 |
| **mMRC** | 0.209 | 0.377 | 0.002 | 0.994 |
| **BMI ($kg/m^2$)** | 0.178 | 0.453 | 0.115 | 0.629 |
| **BODE score** | 0.499* | 0.025 | 0.047 | 0.843 |
| **Combined COPD assessment** | 0.371 | 0.108 | 0.089 | 0.709 |

$r_s$: Spearman coefficient; *: Statistically significant at $p \leq 0.05$

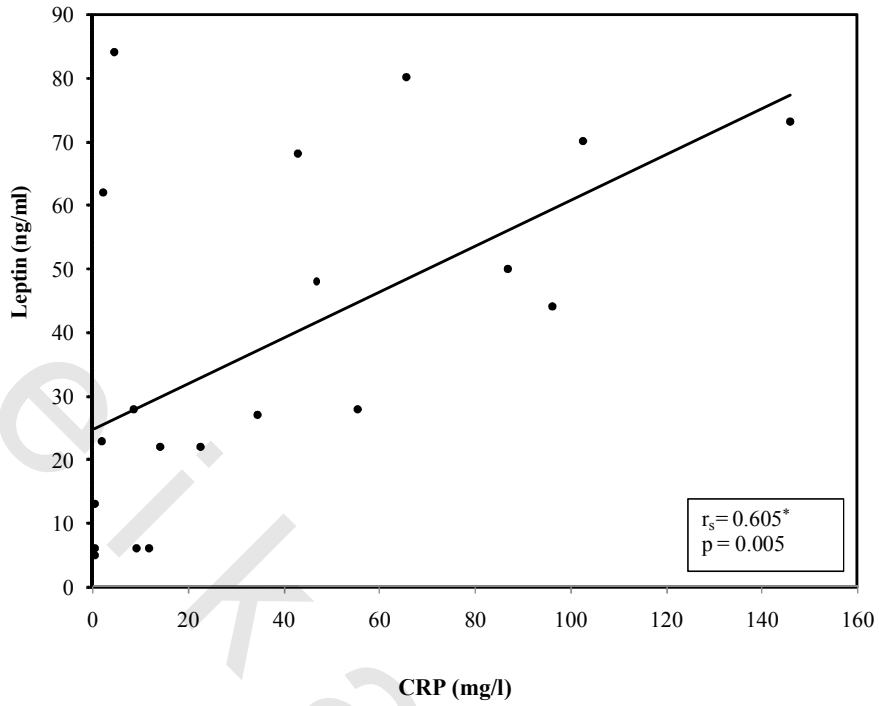


**Figure 32:** Correlation between CRP and leptin in COPD exacerbation subgroup

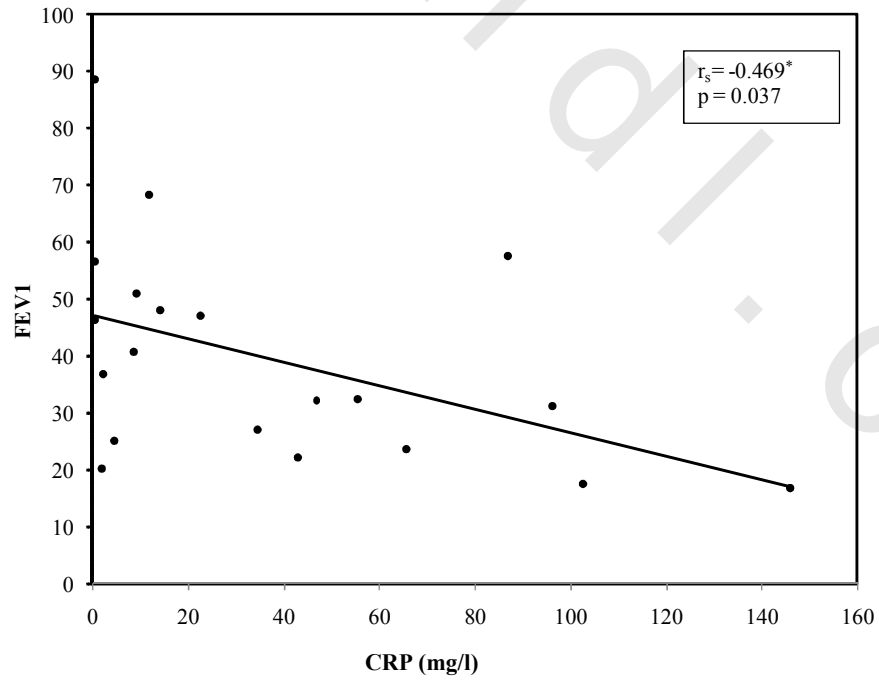


**Figure 33**: Correlation between CRP and FEV1% in COPD exacerbation subgroup

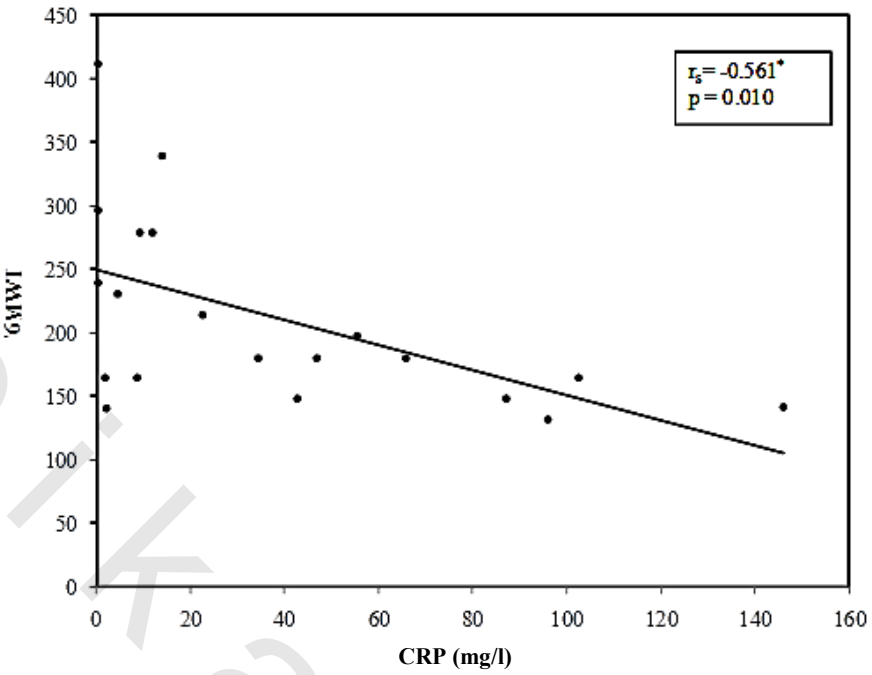


**Figure 34**: Correlation between CRP and 6MWT in COPD exacerbation subgroup

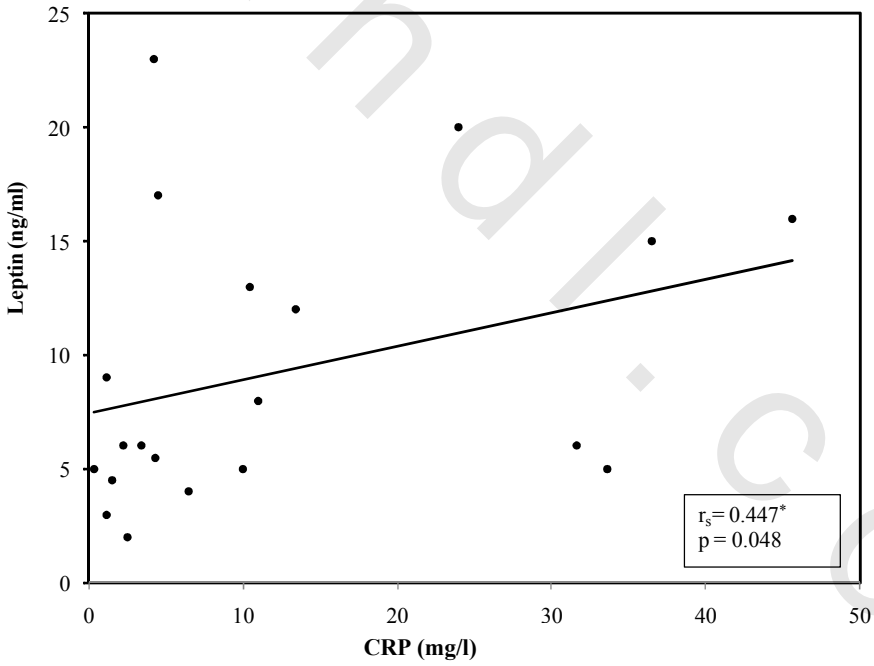


**Figure 35**: Correlation between CRP and leptin in stable COPD subgroup

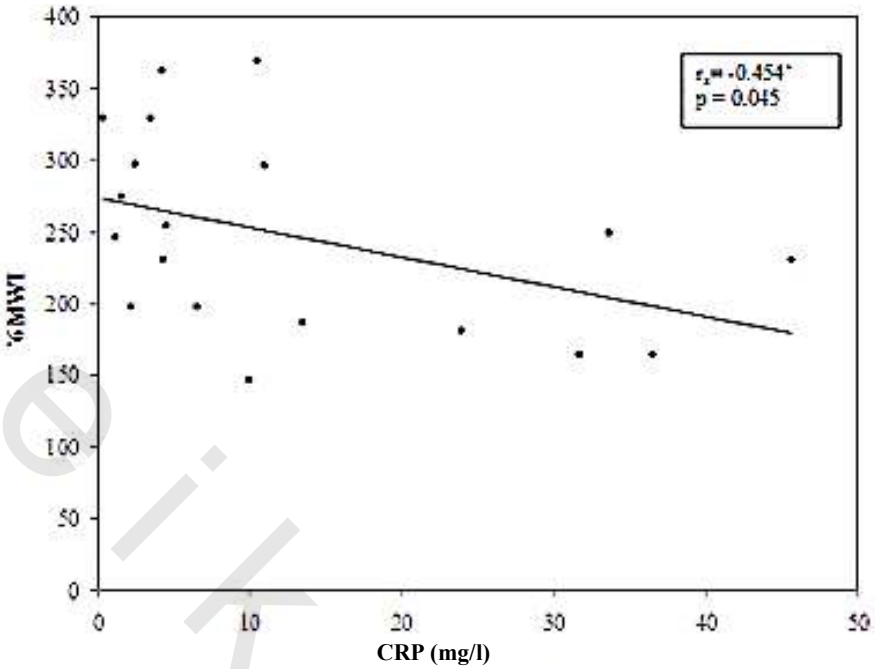


**Figure 36**: Correlation between CRP and 6MWT in stable COPD subgroup

## Correlations of leptin with different studied parameters:

Leptin had been studied for correlations with different studied parameters within the three studied groups; results are shown in (table 21). Results showed the following:

**-For the subgroup A1 (COPD exacerbation):**

- Leptin level showed a positive correlation with CRP level with (r =0.605, p=0.005) (figure 32).
- Leptin level showed a positive correlation with severity assessment by GOLD stages with r=0.689 at p=0.001(figure 37).
- Leptin level showed a positive correlation with the combined COPD assessment groups with r =0.484 at p=0.031(figure 38).
- Leptin level showed a positive correlation with scores of mMRC dyspnea scale (r =0.641, p=0.002) (figure 39).
- Leptin level showed a positive correlation with BODE score (r =0.834, p<0.001) (figure 26).
- In contrast to the previous positive correlations, leptin level showed a negative correlation with predicted FEV1% (r = -0.718, p<0.001) (figure 40). Leptin also showed a negative correlation with 6MWT results (r = -0.680, p=0.001) (figure 41).
- Other variables including FEV1/FVC, smoking index, exacerbation rate and BMI showed no statistically significant correlations with leptin level.

**Table 21: Correlations between leptin and different studied parameters in the study population**

| Leptin (ng/ml) | Subgroup A1 COPD Exacerbation | | Subgroup A2 Stable COPD | | Control group B | |
|---|---|---|---|---|---|---|
| | $r_s$ | p | $r_s$ | p | $r_s$ | p |
| **CRP (mg/l)** | 0.605* | 0.005 | 0.447* | 0.048 | - | - |
| **Smoking index** | 0.136 | 0.643 | 0.406 | 0.150 | - | - |
| **Exacerbation** | 0.002 | 0.993 | 0.027 | 0.909 | - | - |
| **FEV1/ FVC** | -0.408 | 0.074 | 0.004 | 0.987 | - | - |
| **FEV1%** | -0.718* | <0.001 | 0.227 | 0.336 | - | - |
| **GOLD stage** | 0.689* | 0.001 | -0.466* | 0.038 | - | - |
| **6MWT** | -0.680* | 0.001 | -0.032 | 0.922 | - | - |
| **mMRC** | 0.641* | 0.002 | -0.423 | 0.063 | - | - |
| **BMI (kg/m$^2$)** | -0.189 | 0.425 | 0.671* | 0.001 | 0.409* | 0.042 |
| **BODE score** | 0.834* | <0.001 | -0.527* | 0.017 | - | - |
| **Combined COPD assessment** | 0.484* | 0.031 | -0.436 | 0.055 | - | - |

$r_s$: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

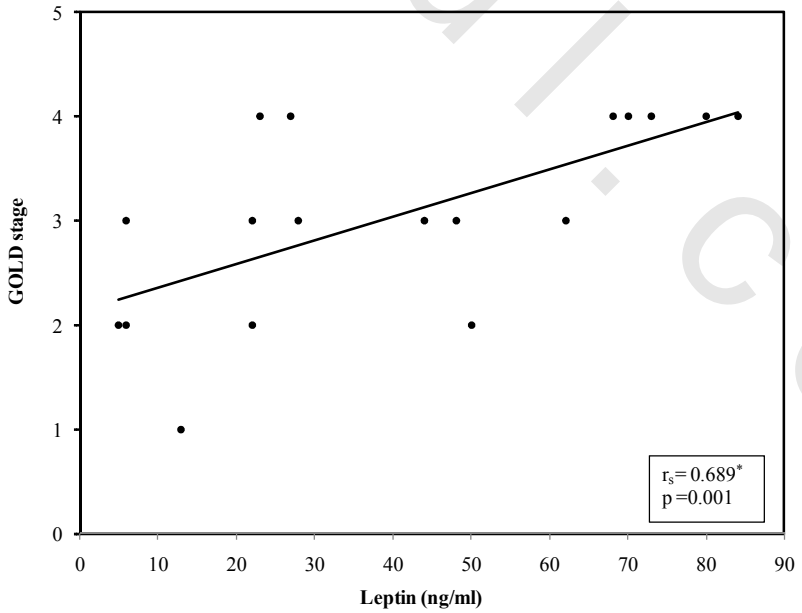


**Figure 37:** Correlation between leptin and GOLD staging in COPD exacerbation subgroup

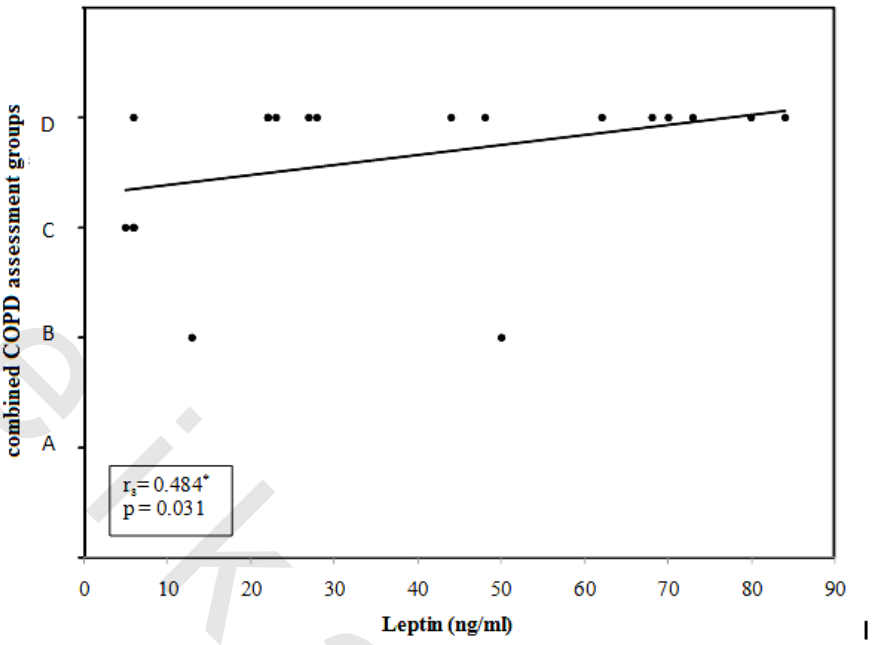


**Figure 38**: Correlation between leptin and combined COPD assessment in COPD exacerbation subgroup

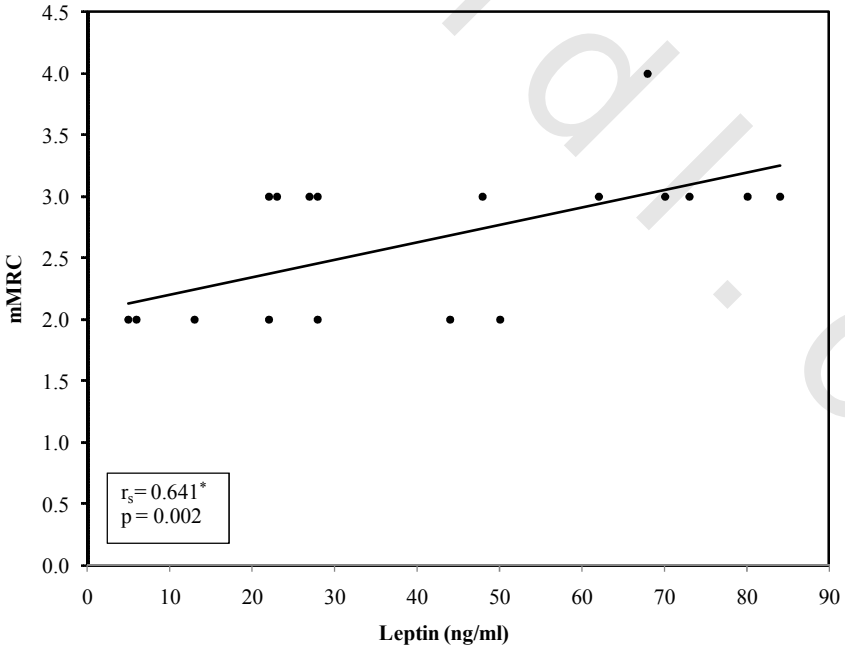


**Figure 39**: Correlation between leptin with mMRC in COPD exacerbation subgroup

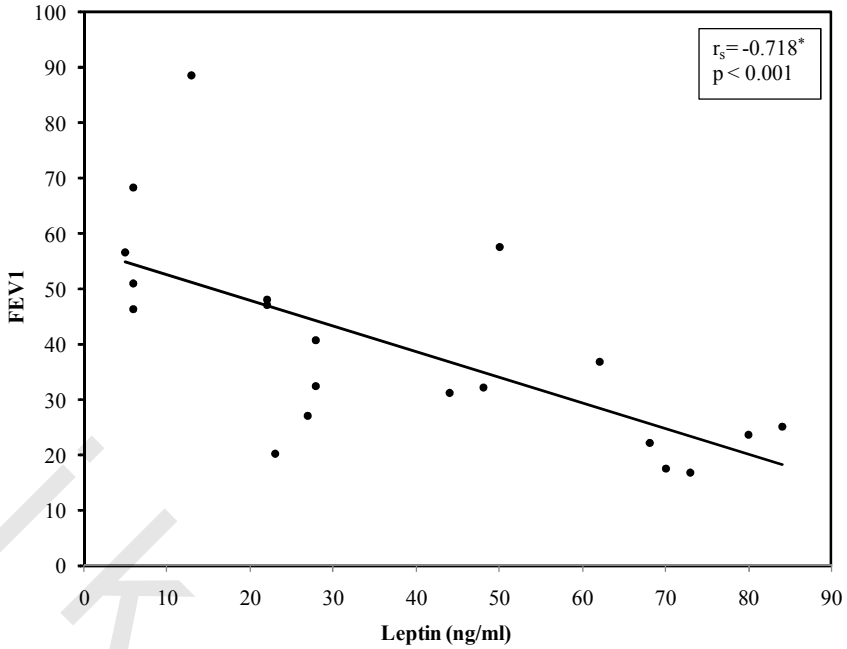


**Figure 40**: Correlation between leptin and predicted FEV1% in COPD exacerbation subgroup

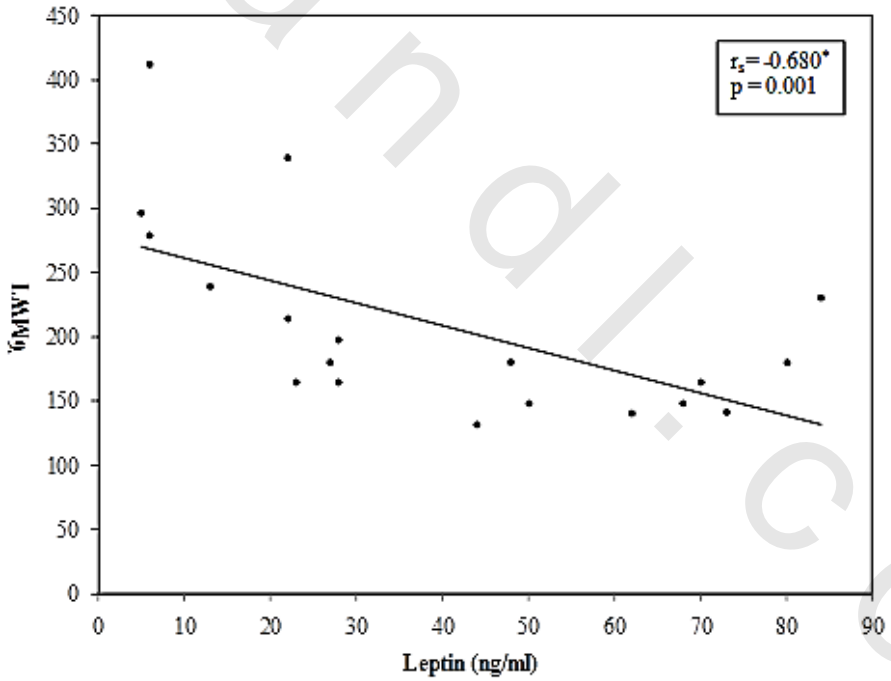


**Figure 41**: Correlation between leptin and 6MWT in COPD exacerbation subgroup

**-For subgroup A2 (stable COPD):**

- Leptin levels showed a positive correlation with CRP level (r=0.447, p=0.048) (figure 35).
- Leptin levels showed a positive correlation with BMI (r= 0.671, p=0.001) (figure 42).
- Leptin levels showed a negative correlation with both GOLD stages (r =-0.446, p=0.038) (figure 43) and BODE score (r =-0.527, p=0.017) (figure 31).
- Other variables including FEV1/FVC, FEV1%, 6MWT and mMRC showed no statistically significant correlations with leptin within this group.

**-For group B (Control group):**

- Leptin levels showed a positive correlation with BMI (r=0.409, p=0.042) (figure 44).

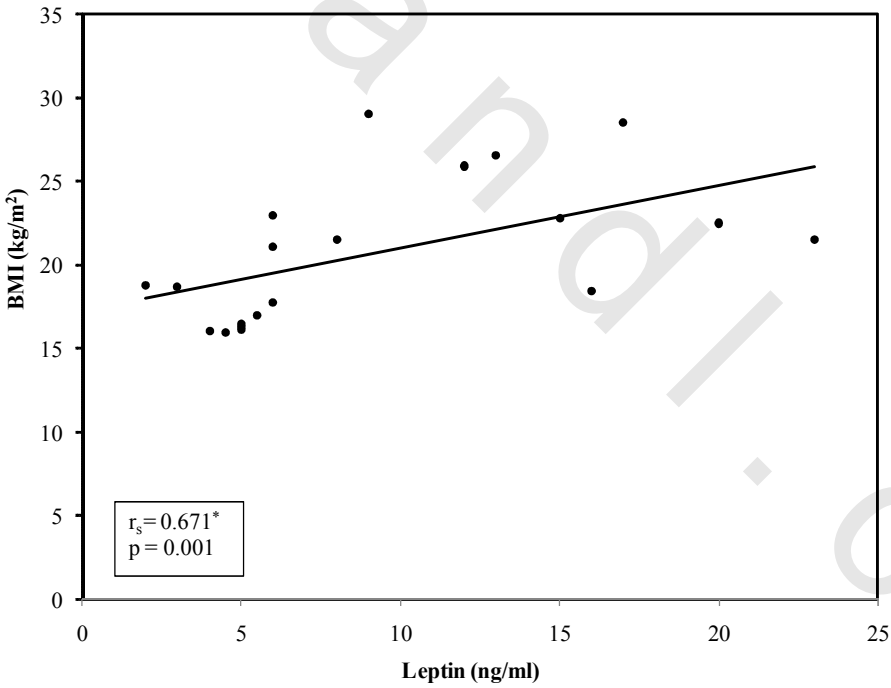


**Figure 42**: Correlation between leptin and BMI ($kg/m^2$) in stable COPD subgroup

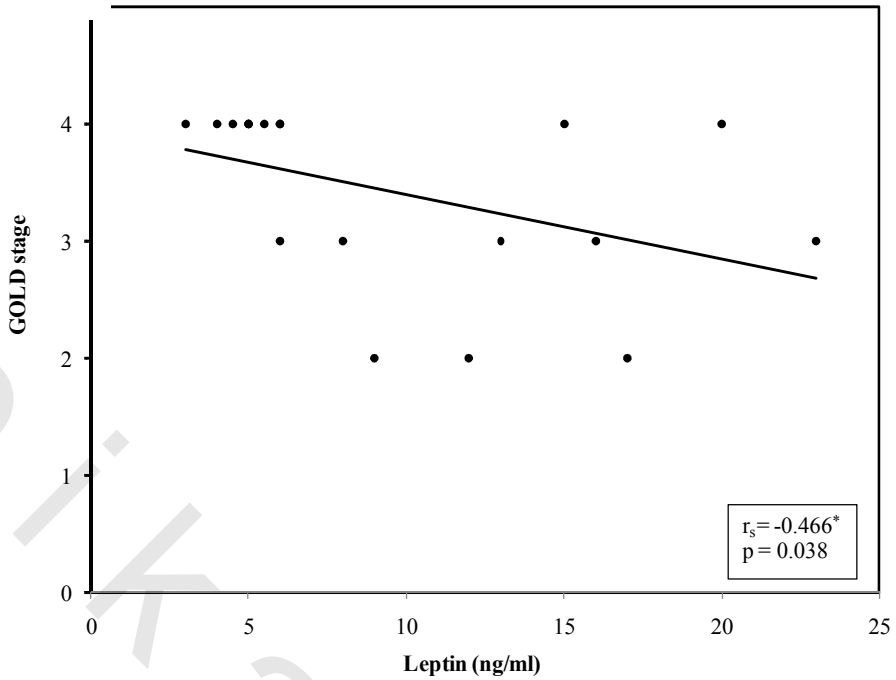


**Figure 43**: Correlation between leptin and GOLD staging in stable COPD subgroup

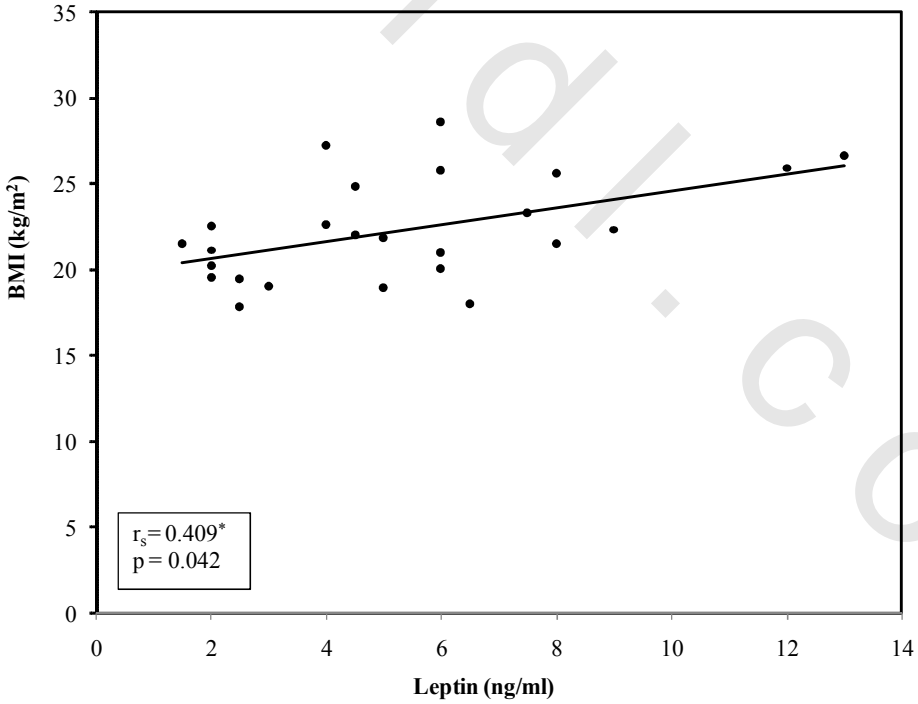


**Figure 44**: Correlation between leptin and BMI in control group B