STUDY OF CHRONIC KIDNEY DISEASE AND ANEMIA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS

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ABSTRACT

The relation between chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) has been largely undescribed and the occurrence and frequency of anemia in COPD has rarely been studied, so **the aim** of this study is: to estimate the frequency of undiagnosed CKD among COPD patients and to verify whether concealed CKD is prevalent in COPD population, and to assess the frequency of anemia in COPD patients and its relation to the severity of the disease. **Patients and methods**: this study included 100 stable COPD patients with various degrees of severity. They were divided into 2 groups: group (I): patients with mild to moderate severity of COPD (n=43) and group (Π): patients with severe to very severe COPD (n= 57). All studied patients were subjected to: pulmonary function tests, complete blood count, erythropoietin level measurement, glomerular filtration rate measurement, and arterial blood gases analysis. **Results:** there was a statistically non- significant increased frequency of concealed chronic renal failure (CRF) in patients of group (Π) than that of group (I). But a significant increased frequency was seen in overt CRF in patients of group (Π) than that of group (I) with a statistically significant positive correlation between COPD severity and renal function reduction . As regards the frequency of anemia, there was a statistically significant high frequency of anemia in patients of group (Π) than that of group (I) with a statistically very highly significant negative correlation between COPD severity and hemoglobin level. **Conclusions:** 1) CRF occurs in high rates in COPD patients and it is related to the disease severity. 2) Anemia is a frequent co-morbidity among COPD patients especially in those with severe disease.

Key words: COPD, chronic kidney disease, anemia.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the major causes of death universal, and it is often associated with other co morbidities **(1).** CKD may be present in patients with mild COPD and can be due to smoking and older age **(2).**The occurrence of both COPD and CKD becomes higher with increasing age and the atherosclerotic disease is present in both diseases **(3).** Anemia became important in COPD during the last ten years only. Anemia in COPD can be caused by different factors. Anemia of chronic disease (ACD) may be the main mechanism of anemia linked with systemic inflammation of COPD which is chronic. Frequency of anemia in general people increases with increasing age and COPD is a disorder affecting the aging persons. So, anemia in COPD may also be linked to the aging process **(4)**. The correlation between COPD and CKD has been largely not represented and very rare studies were done about occurrence and prevalence of anemia in COPD, so **the aim** of this study is: 1) to estimate the frequency of undiagnosed CKD among COPD patients and to verify whether concealed CKD is prevalent in COPD population, and 2) to assess the frequency of anemia in COPD patients and its relation to the severity of the disease.

PATIENTS AND METHODS

This study included 100 COPD patients who were attended to chest outpatient clinic and who were admitted to Chest Department, Zagazig University Hospitals during the period from January 2016 to January 2017.

The mean age of the studied patients was 66.3 ± 7.1 years, they were 81 males and 19 females.

All participants enrolled in this work had to be in a condition of stability and without any symptoms or signs suggesting acute exacerbation or treatment adjustment in the month before including in the study.

An informed written consents were obtained from all patients included in the study.

The patients were diagnosed as COPD patients according to GOLD, 2016.

The patients were classified into 2 groups:

Group (I): patients with mild to moderate severity of COPD (n=43)

Group (Π): patients with severe to very severe COPD (n= 57)

COPD diagnosis: **(5)**

(1) History suggestive of COPD: shortness of breath, chronic cough, chronic sputum production and/or chest wheezes.

(2) Irreversible obstructive airway dysfunction: Post administration of bronchodilator Forced expiratory volume in the first second/Forced vital capacity (FEV1/FVC) < 70%

COPD severity was categorized according to GOLD criteria using the forced expiratory volume in 1 second (FEV1%) predicted into: mild (GOLD stage I; FEV1 ≥ 80% predicted), moderate (GOLD stage Π; 50% ≤ FEV1 < 80% predicted), severe (GOLD stage III; 30% ≤ FEV1 < 50% predicted) and very severe (GOLD stage IV; FEV1 < 30% predicted) **(5).**

Inclusion criteria:

This study included adults aged 59 to 74 years, diagnosed with COPD with various degrees of severity.

Exclusion criteria:

Bronchial asthma, history of malignancy or hematological disorder, history of gastrointestinal or other hemorrhage, autoimmune disorder, heart failure, mental impairment, liver cirrhosis, the use of oral corticosteroids, thyroid disease, blood transfusion in the last 4 months, pregnancy, and long term oxygen therapy **(6,7).**

Methods:

All studied patients were subjected to the followings:

1) Thorough medical history stressing on smoking history.

2) General and local examination.

3) Chest X- ray (posteroanterior and lateral views).

4) Electrocardiogram (ECG).

5) Pulmonary function tests (PFTs): FEV1% predicted and FEV1/FVC were measured using Wins Piro PRO 5.0.0 apparatus.

6) Laboratory investigations:

a) Complete Blood Count (CBC).

Diagnosis of anemia was made by hemoglobin (Hb) levels < 13.5 g/dL for male patients and < 12 g/dL for female patients **(8).**

b) Erythropoietin (EPO) measurement: **(9)**

Determination of human serum EPO by ELISA (ALPCO, USA)(Catalog No. 21- APOHU- E01). The specimens were collected between 7: 30 a.m. to 12: 00 noon, because of variation of EPO levels during the day has been recorded in the literature. The sample is whole blood without anticoagulant and allow blood to clot between 2 – 8°C. Then, separation of the serum should be rapidly, in a centrifuge which is refrigerated and storage at -15°C or lower. The normal range in adult were 3.22 – 31.9 U/L.

c) Liver function test.

d) Blood sugar (fasting and 2 hours post prandial).

e) Lipid profile.

f) Kidney function test:

- Urea and creatinine.
- Glomerular filtration rate (GFR): **(10)**

The GFR was evaluated using the Modification of Diet in Renal Diseases (MDRD) Study Group equation:

$170 \times [\text{Serum creatinine}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{blood urea}]^{-0.170} \times [\text{serum albumin}]^{-0.318} \times (0.762 \text{ for women}) \times (1.180 \text{ for African- American subjects})$.

Patients were classified according to their kidney function as having normal renal function (GFR ≥ 60 mL/min/1.73 m^2), concealed chronic renal failure (CRF) (normal serum creatinine and GFR < 60 mL/min/1.73m^2) or overt CRF (increased serum creatinine and GFR < 60 mL/min/1.73 m^2). The cut-off value for serum creatinine was 1.26 mg/dL for men and 1.04 mg/dL for women.

Chronic kidney disease (CKD): is defined as the persistence of reduction in kidney function to a GFR < 60 mL/min/1.73 m^2 of findings suggestive of renal impairment (e.g. proteinurea) for 3 months or more **(11).**

g) Arterial blood gases (ABGs) analysis:

Measurement of pH, PaO2, PaCO2, SaO2 using blood gas analyzer (ABL- 330- Radiometer Copenhagen).

Statistical analysis: was performed with the SPSS statistical software package (SPSS Inc., Chicago, IL).

Data presented by mean ± SD for quantitative continuous data was calculated by one way analysis for variance (F test).

Qualitative data was presented by number and percentage and association was tested by Chi – square test.

Pearson Chi – square test was used for qualitative data and Fisher Exact test was recommended when expected cell is less than five. P- value < 0.05 is considered significant.

Correlation coefficient (r) were calculated for testing association between quantitative variables. P- value < 0.05 is considered significant.

RESULTS

Table (1): Demographic data of all studied COPD patients and various severity degrees

Parameter	Total (n=100)	Group (I) (n=43)	Group (II) (n=57)	P- value
Age (years)(M±SD)	66.3 ± 7.1	65.8 ± 7.3	67.4 ± 7.6	0.28
Sex, no.(%):				
- Male	81 (81%)	33 (76.74%)	48 (84.2%)	0.18
- Female	19 (19%)	10 (23.26%)	9 (15.8)	
PFTs (M±SD):				
- FEV1/FVC	59.32 ± 15.63	60.72 ± 15.92	52.83 ± 15.28	0.01
- FEV1% predicted	54.51 ±13.18	65.13 ± 13.71	48.32 ± 10.16	0.00
Smoking, no.(%):				
- Non- smoker	22 (22%)	13 (30.2%)	9 (15.79%)	0.03
- Ex-smoker	66 (66%)	25 (58.1%)	41 (71.9%)	0.22
- Current smoker	12 (12%)	8 (18.6%)	4 (7.02%)	0.027
Co morbidities, no.(%):				
- Diabetes mellitus (DM)	15 (15%)	3 (6.98%)	12 (21.1%)	0.007
- Hypertension	29 (29%)	11 (25.6%)	18 (31.6%)	0.42
- Dyslipidemia	15 (15%)	6 (13.95%)	9 (15.79%)	0.74
- Cardiovascular disease (CVD)	23 (23%)	8 (18.6%)	15 (26.3%)	0.25
- Stroke	1 (1%)	0 (0.0%)	1 (1.75%)	0.56

Table (2): Laboratory data in all studied COPD patients and in various degrees of severity

Parameter	Total (n=100)	Group (I) (n=43)	Group (II) (n=57)	P- value
- GFR (mL/min/1.73 m^2) (M ± SD)	47.2 ± 4.5	53.6 ± 4.9	36.7 ± 2.1	0.00
- Normal kidney function, no.(%)	24 (24%)	21 (48.8%)	3 (5.3%)	0.00
- Concealed CRF, no.(%)	55 (55%)	20 (46.5%)	35 (61.4%)	0.14
- Overt CRF, no.(%)	21 (21%)	2 (4.7%)	19 (33.3%)	0.00
- Serum creatinine (mg/dl) (M ± SD)	1.39 ± 0.63	0.85 ± 0.33	1.9 ± 0.64	0.002
- Microalbuminurea, no.(%)	53 (53%)	20 (46.5%)	33 (57.9%)	0.27
- Hb (g/dl)(M ± SD):				
Male	13.3 ± 0.5	12.6 ± 1.2	10.4 ± 1.3	0.0001
Female	12.5 ± 0.4	12.1 ± 1.1	10.3 ± 1.3	0.00
- EPO (U/L) (M ± SD)	49.2 ± 13.2	47.3 ± 13.1	57.7 ± 14.1	0.0002
- ABG (M ± SD)				
pH	7.41 ± 0.03	7.42 ± 0.03	7.39 ± 0.02	0.11
PaO2 (mmHg)	76.3 ± 11.8	77.5 ± 14.7	75.2 ± 11.3	0.36
PaCO2 (mmHg)	44.6 ± 2.3	43.4 ± 2.5	47.5 ± 3.1	0.0001
SaO2 (%)	93.5 ± 2.1	94.2 ± 2.3	92.3 ± 2.8	0.001

Table (3): Frequency of CRF and anemia in all studied patients and in various degrees of severity

	Total (n=100)	Group (I) (n=43)	Group (II) (n=57)	P- value
Frequency of CRF, no. (%)				
- Concealed CRF (n=55)	55 (55%)	20 (46.5%)	35 (61.4%)	0.14
- Overt CRF (n=21)	21 (21%)	2 (4.7%)	19 (33.3%)	0.00
Frequency of anemia, no. (%)	33 (33%)	10 (23.3%)	23 (40.4%)	0.032

Table (4): Correlation between renal function reduction and COPD severity

	Renal function reduction	
COPD severity	R	P
	0.37	0.02

Table (5): Correlation between Hb level and COPD severity

	Hb level (g/dl)	
COPD severity	**R**	**P**
	- 0.88	**0.00**

Table (6): Distribution of different data among COPD patients regarding GFR measurement

Parameter	Normal (n=24)	Concealed CRF (n= 55)	Overt CRF (n=21)	P- value
Age (years) (M±SD)	65.6 ± 2.8	66.9 ± 3.2	67.21 ± 3.5	0.17
Sex, no.(%)				
Male	16 (66.7%)	46 (83.6%)	19 (90.5)	0.096
Female	8 (33.3%)	9 (16.4%)	2 (9.5%)	
Smoking, no.(%)				
Non- smoker	7(29.2%)	15 (27.3%)	0 (0.0%)	
Ex- smoker	16 (66.7%)	35 (63.6%)	15 (71.4%)	0.014
Current smoker	1 (4.2%)	5 (9.1%)	6 (28.6%)	
FEV1% predicted (M±SD)	57.9 ± 17.1	56.1 ± 18.3	53.7 ± 12.4	0.69
Hb (g/dl)(M±SD):				
Male	13.1 ± 3.8	12.5 ± 3.1	10.5 ±2.6	0.018
Female	12.2 ± 2.9	12 ± 2.8	10.2 ± 2.5	0.031
Serum creatinine (mg/dl) (M±SD)	0.84 ± 0.3	1.1 ± 0.7	2.1 ± 0.9	0.00
Microalbuminurea, no.(%)				
EPO (U/L)(M±SD)	0 (0.0%)	34 (61.8%)	19 (90.5%)	0.00
pH	47.6 ± 12.9	49.3 ± 12.3	56.4 ± 13.5	0.029
PaO2 (mmHg)	7.42 ± 0.03	7.42 ± 0.01	7.41 ± 0.01	0.76
PaCO2 (mmHg)	78.5 ± 12.3	76.3 ± 12.1	74.1 ± 11.3	0.42
SaO2 (%)	44.7 ± 2.5	43.1 ± 2.6	47.2 ± 2.8	0.001
Co morbidities, no.(%):	94.2 ± 3.1	93.5 ±3.6	92.7 ± 3.3	0.37
DM				
Hypertension	3 (12.5%)	3 (5.5%)	9 (42.9%)	0.00
Hyperlipidemia	5 (20.8%)	11 (20%)	13 (61.9%)	0.00
CVD	2 (8.3%)	6 (10.9%)	7 (33.3%)	0.00002
Stroke	5 (20.8)	10 (18.2%)	8 (38.1%)	0.01
	0 (0.0%)	0 (0.0%)	1 (4.8%)	0.04

Table (1) showed the demographic data of all studied patients. Table (2) showed a statistically very highly significant decrease in GFR (mL/min/1.73 m^2) in COPD patients in group (Π) than that in those of group (I) (P= 0.00). Also a statistically high significant increase in serum creatinine (mg/dl) was found in patients of group (Π) than in those of group (I) (P= 0.002). Regarding renal function , there was a statistically highly significant high number of patients who had normal kidney function in group (I) than that in group (II), but the reverse was found as regards concealed and overt CRF. While microalbuminurea was found in patients of both groups with statistically non- significant difference (P= 0.27) when comparison was done between them. As regards Hb level (g/dl), there was statistically very highly significant decrease in it in both male and female patients of group (Π) than that in group (I) (P= 0.00). But the EPO level showed very highly significant increase in its level in patients of group(Π) than that of group (I) (P= 0.0002). Table (3) showed that there was a statistically non- significant increased frequency of concealed CRF (P=0.14) but significant increased frequency was seen in overt CRF (P=0.00) in patients of group (Π) than that of group (I). As regards the frequency of anemia, there was a statistically significant high frequency of anemia in patients of group (Π) than that of group (I) (P= 0.032). Table (4) showed a statistically significant positive correlation between COPD severity and renal function reduction (P= 0.02). Table (5) showed a statistically very highly significant negative correlation between COPD severity and hemoglobin level (g/dl) (P= 0.00). Table (6) showed a statistically significant decrease in hemoglobin level (g/dl) in overt CRF group than that in concealed CRF and normal kidney function groups (P< 0.05) in both male and female patients. But serum creatinine (mg/dl) showed increased level in overt CRF group than that in other groups and this increase was very highly significant statistically (P= 0.00). Regarding EPO, there was a statistically significant increase in its level (P=0.029) in overt CRF group than that in the other groups. There was a statistically significant increase in percentages of ex- smokers and current smokers in overt CRF group than that in

concealed CRF and normal kidney function groups. And also there was a statistically significant high percentage of presence of microalbuminurea in overt CRF group than that in concealed CRF and normal kidney function groups (P=0.00). As regards PaCO2, there was a statistically very highly significant elevation in its level in overt CRF group than that in concealed CRF and normal kidney function groups (P=0.001). Also regarding the co morbidities, there were statistically significant high percentages of co morbidities in overt CRF group than those in concealed CRF and normal kidney function groups (P<0.05).

DISCUSSION

Earlier stage of CKD is a frequent co morbidity in COPD patients. This is probably partly due to sharing of risk factors, but it has been proposed that chronic low- grade inflammation could be a link between COPD and CKD **(12)**. Kidney function affects mortality of COPD patients. Up till now, restricted evidence is accessible on the effect of CKD on long term survival of patients with COPD. There are studies denote the COPD is a known risk factor for the CKD evolvement **(13).** In recent years, anemia has become another co morbidity that became important in patients with COPD **(4).** Anemia is undervalued issue in COPD, but it is so important in this disease **(14).** So the aim of this work is: 1) to estimate the frequency of undiagnosed CKD among COPD patients and to verify weather concealed CKD is prevalent in COPD population, and 2) to assess the frequency of anemia among COPD patients and its relation to the disease severity. In this study, there was a statistically very highly significant decrease in GRF level in group (Π) than that in group (I) (Table 2) with a statistically non- significant increase in concealed CRF frequency in group (Π) (61.4%) than that in group (I) (46.5%) with overall percentage of frequency was 55% in all studied COPD patients (Table 3). But this increase in frequency was statistically very highly significant in group (Π) (33.3%) than that in group (I) (4.7%) as regards overt CRF with overall percentage of frequency was 21% in all studied COPD patients (Table 3). Also there was a statistically significant positive correlation between COPD severity and renal function reduction (Table 4). Many risk factors for CKD are present in general with COPD, as advanced age, smoking and this indicates that CKD is linked to the underlying inflammation which is chronic. Though there is no attention to CKD as a co morbidity of COPD, there are in recent years several studies observing that CRF and microalbuminurea appear in a high rate among patients with COPD, suggesting relationship between COPD and CKD **(15)**. COPD strengthens the development of CKD via a mechanism which remains unclear. Many suppositions have been put forward. It might be linked to the truth that COPD is mainly a disorder of the older people who have co- morbidities such as DM, hypertension and CVD, known risk factors related to CKD. COPD has been characterized by inflammation which is systemic **(16)**. The mechanisms that link emphysema and kidney function remain speculative. Emphysema leads to right ventricular volume overload by increasing pulmonary vascular resistance (PVR) reducing the cardiac output and renal perfusion with resultant reduction in GFR. Another possible mechanism via the cellular and immune complex mediated systemic inflammatory response among emphysema **(17)** similar to other inflammatory disorders**.** The association between COPD and CRF may be explained by several factors. First, it was found that the renal resistances in arterioles are elevated in COPD patients, may be due to local adrenergic discharge as a result of hypercapnia. In the initiative phase of COPD, there is normal kidney perfusion, but as the condition progresses, especially with development of CO2 retention, renal perfusion reduces. CO2 retention may lead to renal vasoconstriction directly and indirectly through stimulation of sympathetic tone which observed by the rise of levels of nor-epinephrine in the circulation **(18)**. Second; COPD as a chronic inflammatory disease usually recognized as a source of systemic inflammatory mediators, namely tumor necrosis factor alpha (TNF-α), which play a crucial role in the disease process. The systemic inflammatory status in COPD patients is associated with inflammation in several body organs resulting in muscle wasting, weight loss, DM, osteoporosis, atherosclerosis and kidney dysfunction. So the persistent systemic inflammation in COPD patients can explain the prevalence of CRF among COPD patients **(19)**. Also, as a result of the muscle wasting and reduced muscle mass that is frequently occurring in COPD patients: serum creatinine may be falsely lowered due to diminished creatine release and the GFR may be reduced despite normal creatinine concentration (concealed CRF) **(20)**. It is possible that kidney injury occurs due to damage of the blood vessels by the inflammatory mediators, increasing the risk of CKD occurrence. COPD patients are more prone to kidney injury especially the hypoxemic patients and renal-endocrine pathway, diminished tissue oxygenation, vascular sclerosis also play a role in the pathophysiology **(21)**. **Incalzi et al. (20)**

found that the frequency of CRF in their COPD patients was 43% (20.8% concealed CRF and 22.2% overt CRF) and this result of overt CRF was near our result. **Mapel and Marton (22)** agreed our result as they found increased prevalence of renal dysfunction in stable COPD patients and these patients are at high risk of both acute and chronic kidney injury. Also **Fedeli et al. (23)** found that the renal impairment occurred frequently as a co morbid condition in COPD patients, observed in 10.2% of patients, particularly if they age ≥ 75 years. Our result is found to be higher than the above results and this difference may be explained by the high number of severe to very severe COPD patients in our study and also smoking and the high age of our patients made them more exposed to CKD than other patients. Regarding COPD severity, **Chandra et al. (24)** reported that estimated GFR and serum creatinine correlated with the severity of emphysema noted on CT scan and this result agreed our result (Table 4). In disagreement to our result, **Chen and Liao(13)** found no significant correlation between CKD and severe COPD. This difference between the above results and our result may be explained by the higher death rate in the most severe COPD group in their studies. Regarding smoking, this study showed 66% ex- smoker and 12% current smoker (Table 1) with a statistically highly significant increase in percentages of ex- smokers and current smokers in overt CRF group than those in concealed CRF group (Table 6). Smoking plays a major role in the development and progression of both COPD and renal disease **(25). Fox et al. (26)** found that advanced age, body mass index, DM, cigarette smoking and hypertension have formerly been known as risk factors for new- onset renal disease. Selected heavy metals as lead and cadmium and nicotine which are constituents of tobacco, are major risk factors for development of CRF. Nicotine causes nephropathies with an increased incidence of microalbuminurea progressing to proteinurea. In this study, there was microalbuminurea in 53% of all studied COPD patients (Table 2) with a statistically very highly significant increase in percentage of patients who had microalbuminurea in overt CRF group than that of patients in concealed CRF group (Table 6). COPD is accompanied with micro-albuminurea and in patients with hypoxemia and hypercapnia, effective renal perfusion became reduced. These changes may reflect increased activity of rennin- angiotensin system present in COPD patients. In the Multi- Ethnic Study of Atherosclerosis cohort, Harris et al. found an reverse correlation between FEV1 and FVC with urinany albumin excretion and urine albumin to urine creatinine ratio. This finding supposes that injury of systemic microvasculature may lead to appearance of CKD in patients with COPD**(27)**. In this study, there was a statistically very highly significant decrease in Hb level in both male and female patients of group (Π) than that in those of group (I) (Table 2) with a statistically significant increase in anemia frequency in group (Π) (40.4%) than that in group (I)(23.3%) with overall frequency of anemia in all studied COPD patients was 33% (Table 3). Also there was a statistically very highly significant negative correlation between COPD severity and Hb level (Table 5). A statistically significant decrease in Hb level was found in overt CRF group than that in concealed CRF group (Table 6). Regarding EPO, there was a statistically significant increase in EPO level in group (Π) than that in group (I) (Table 2) and in overt CRF group than that in concealed CRF group (Table 6). Most common type of anemia seen in COPD is that of chronic disease (ACD) and inflammation. The mechanism by which anemia develops in COPD may be similar to that occurs in other chronic diseases. Mediators of inflammation as IL-6, TNF-α, and interferon-gamma are involved in the development of anemia of chronic disease. From a view of pathophysiology, there were 3 possible mechanisms thought to cause ACD: 1) Shortened survival of RBC. 2) Dysregulation of iron homeostasis and impaired metabolism, 3) Impaired bone marrow EPO response **(28)**. The 3 mechanisms are inter-related to each other. The bone marrow cannot sufficiently respond to the elevated need for RBCs. This is caused by relative resistance of EPO because of weakened capability of RBCs progenitors to react to EPO **(29)**. The elevation of cytokines can lead to hepcidin-stimulated failure of iron which was absorbed from the gut and hepcidin- stimulated accumulation of iron stores in the macrophages and hepatocytes **(30)**. CRF is a known cause of anemia. Studies have observed the development of CRF as a co morbidity in COPD patients and may explain the presence of anemia in COPD. CRF can lead to anemia by insufficient production of EPO by proximal convoluted cells **(20,31).** It has been noticed that use of angiotensin converting enzyme inhibitor (ACEI) can lead to reduction of EPO activity in the bone marrow. Like ACEI which reduces hematocrit values, theophylline also leads to a reduced production of RBCs **(32)**. It must be confirmed that factors other than inflammation can cause anemia in patients with COPD. Tobacco smoking (because of its associated oxidative stress), oxygen therapy and

malnutrition can academically inhibit hypoxia-induced erythropoiesis in patients with COPD**(33)**. In concordance with our results, **Nowinski et al. (34)** recorded that the prevalence of anemia in COPD changes broadly and expands between 4.9% and 33% which is comparable to our result. And **Yohannes and Ershler (35)** found that anemia is a common co morbid condition in COPD having prevalence rate of 5% to 30%. Also **Khandelwal et al. (6)** found that anemia was present in almost 42.3% of all COPD patients. In disagreement of our result, **Parveen et al. (36)** found that the frequency of anemia in COPD patients was 18% and 12.3% in **Ferrari et al. (7)** study which are less than our result. The difference between our result and the above results and the wide range of the frequency of anemia in COPD may be due to different items, such as some studies which are retrospective, use of different populations (COPD in exacerbated or stability phase; outpatients or inhospital patients, the use of several cut-off levels of Hb to define anemia and the presence of confusing factors such as the presence of many other reasons of anemia like renal failure, neoplasm, heart failure, etc. Regarding severity of COPD, **Barnes and Celli (37)** agreed our result of anemia prevalence in severe to very severe COPD patients (40.4%) and their study result showed that anemia is a common co morbid disease in COPD, ranging from 10 to 30% of COPD patients particularly severe COPD and this result is close to our finding. **Portillo et al. (38)** suggested that the rate of anemia is likely elevated in severe COPD when comparison was done between them and general COPD patients. In discordance to our result, **Similowski et al. (30)** suggested that anemia in COPD patients may be more common than expected, presents in 10- 15% of COPD patients who have severe forms of the disease. And **Casanova et al. (39)** found that patients who had anemia tend to have more severe form of COPD in terms of FEV1, with a prevalence of anemia in cases with very severe COPD near 9%. The difference between our result and the above studies results may be explained by the high number of severe to very severe COPD patients in our study, so the frequency of anemia among them was high. In concordance with our result of the significant negative correlation between COPD severity and Hb level affection (Table 5), **Chambellan et al. (33)** observed that there was a relationship between anemia and other factors like BMI, age, blood gas analysis and COPD severity. Also, **Yohannes and Ershler (36)** found that the frequency of associated anemia in COPD patients is highly different and depends on disease severity. **Esquinas and Confalonieri (40)** observed that the prevalence of anemia varied according to COPD severity. There was an inverse association with FEV1 value and severity of anemia, indicating a possible link between Hb and functional status. **Khandelwal et al. (6)** study showed decrease in Hb level in COPD patients affect both dyspnea scoring and COPD severity on spirometry (FEV1 value). **Zavarreh and Zahmatkesh(41)** disagreed our result as they found that there was no significant relation between anemia and the severity of COPD. As regards EPO, **John et al. (42)** study showed that anemic COPD cases had elevated levels of EPO which may indicate the presence of EPO resistance. Inflammatory cytokines reduce the response of EPO to decreased arterial oxygen, prevent iron usage and weaken the response of bone marrow to EPO.

Conclusions:

1) CRF occurs in high rates among COPD patients and it is related to the disease severity.

2) Anemia is a frequent co-morbidity among COPD patients especially in those with severe disease.

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