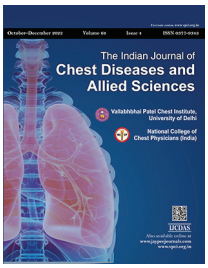
ORIGINAL ARTICLE

# Potential Impact of Anemia and Iron Deficiency in Chronic Obstructive Pulmonary Disease Patients and its Relation to Serum Levels of Erythropoietin

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## Abstract

**Background:** Little is known about iron deficiency (ID) and anemia in chronic obstructive pulmonary disease (COPD). To study the prevalence and treatment of anemia in patients of COPD and to check the hemoglobin level in all patients with COPD and to assess the quality of life (QOL) by administering the questionnaire in anemic COPD patients and comparing it with nonanemic COPD patients.

**Methods:** We examined the subjects and administered a questionnaire based on dyspnea score to assess the impact of anemia on quality of life in patients of COPD. A total of 250 COPD patients were enrolled in the study, in that 62 patients were anemic and 188 patients were nonanemic in COPD patients.

**Results:** The proportion of patients of nonanemic was found to be higher as compared with anemia having modified medical research council (mMRC) grade I (35.71% vs 20.00%), grade II (40.48% vs 26.67%), and grade IV (11.90% vs 6.67%), while the proportion of patients of anemia was found to be higher than that of nonanemic having mMRC grade III (46.67% vs 11.90%). Difference in mMRC grade of patients of anemia and nonanemic was found to be statistically highly significant. Out of 250 patients of COPD, hemoglobin levels of 62 (26.32%) were found to be below normal levels and were diagnosed as anemic and classified as anemia in the present study, while hemoglobin levels of the rest 188 (73.68%) patients were found to be normal and were classified as nonanemic. Prevalence of anemia in COPD = 24.87%.

**Conclusion:** Anemia occurs frequently in patients of COPD and is associated with poor quality of life and increased morbidity in the form of number of exacerbations and hospital admissions. Correcting anemia in these patients may improve their clinical outcomes.

**Keywords:** Anemia, Chronic obstructive pulmonary disease, Erythropoietin, Iron deficiency, Renal failure.

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## Abbreviations used in this Article

ID = Iron deficiency; COPD = Chronic obstructive pulmonary disease; RBC = Red blood cell; ACD = Anemia of chronic disease; QOL = quality of life; EPO = Erythropoietin; GOLD = Global initiative for chronic obstructive lung disease; FVC = Forced vital capacity; FEV = Forced expiratory volume; mMRC = Modified medical research council; SD = Standard deviation; BMI = Body mass index; 6MWD = 6-minute walk distance; TNF-α = Tumor necrosis factor-α; IL-6 = Interleukin-6.

## Introduction

Many chronic diseases have been shown to affect hematopoiesis, resulting in shortening of red blood cell (RBC) lifespan and sequestration of iron in macrophages, leading to so-called anemia of chronic disease (ACD). Over the past years, the clinical scope of this syndrome has stretched beyond its traditional chronic infectious, inflammatory, and neoplastic causes, including heart failure. Theoretically, COPD is another candidate likely to be associated with ACD, when considered in relation to already-known systemic effects of the disease.[1] Exacerbations and comorbidities add to the overall severity in individual patients. Some of the common comorbidities that add to the expanded hazard related to morbidity and mortality in COPD patients incorporate cardiovascular diseases, hypertension, diabetes, hypercholesterolemia, osteoporosis, gastroesophageal reflux, and anemia. Other comorbidities can be clinical depression and anxiety. The specific reason for these comorbidities is at present obscure, however, recent studies and research indicate that systemic inflammation is associated with their development.[2]

The variables that have been connected to systemic consequences and comorbidities in COPD patients are systemic inflammation and shared risk factors, smoking, and physical inactivity/deconditioning of late iron deficiency has become

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another comorbidity that has picked up significance in patients with COPD. Polycythemia is a common adverse event of hypoxemia in COPD. In any case, these days, this happens less every now and again because of progressively thorough rectification of hypoxemia by domiciliary long-term oxygen therapy.[3] Then again, iron deficiency has been accounted for all the more much of the time in relationship with COPD as of late with an effect on the QOL, healthcare utilization, and survival. Many chronic diseases have been shown to affect hematopoiesis, resulting in shortening of RBC lifespan and sequestration of iron in macrophages, and leading to so-called ACD. Anemia of chronic disease is immune-driven and mainly inflammatory in nature, several cytokines and chemokines are involved in the mechanism leading to ACD and interfere in hematopoiesis, having a key role in ACD.

The physiologic regulator of red cell production erythropoietin (EPO) is produced and released by peritubular capillary lining kidney cells. Exacerbations of COPD are associated with worsening of lung function, decreased QOL, increased systemic inflammation, and have a significant impact on survival.[4]

Although the precise mechanism of anemia in COPD patients is unknown, there appears to be a relationship with certain pro-inflammatory markers. Various studies have indicated an inverse or negative correlation between the hemoglobin and EPO concentration, which suggests that in COPD patients, low hemoglobin correlates with compensatory EPO response. So we had planned to evaluate the prevalence of anemia in patients with COPD and its impact on QOL. Second, to check the hemoglobin level in all patients with COPD and to assess the QOL by administering the questionnaire in anemic COPD patients and comparing it with nonanemic COPD patients.

## Materials and Methods

The present study is cross-sectional and was conducted at a tertiary care teaching hospital of North India. Total 250 newly diagnosed patients from 30 to 80 years suffering from COPD attending the Department of Pulmonary Medicine as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2018[5] were included in the study. The written informed consent was obtained fulfilling the inclusion and exclusion criteria of the study. The study was approved by the Institutional Ethics Committee, Ref code no. 62 ECM II-B/P5. We studied the prevalence of anemia in patients with COPD and its impact on quality of life. Demographic data of the patients were collected through an interview, and anthropometric variables were noted as per standard protocol. All the patients were subjected to thorough clinical examination along with laboratory investigations and X-ray chest. All the subjects were administered a questionnaire based on dyspnea score to assess the impact of anemia on quality of life in patients of COPD. The diagnosis of COPD was based on pulmonary function test that was done in all patients. According to the GOLD criteria, COPD was defined on the basis of the post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio of <0.70 and reversibility to an inhaled bronchodilator in FEV1 <12% or <200 mL after administration of 200 µg of salbutamol (2 puffs) using a pressurized metered-dose inhaler with a spacer. The GOLD system categorizes airflow limitation into four stages in patients with FEV1/FVC < 0.70.

Anemia was defined according to the WHO criteria as hemoglobin level <13 gm/dL in men and 12 gm/dL in women. Chronic obstructive pulmonary disease patients were divided into two groups: anemic (group II) and nonanemic (group II) on the basis of this definition. Patients reporting with a history of pulmonary tuberculosis, cardiac diseases, interstitial lung disease, pregnancy, diabetes, and cancer were excluded from the study. Patients with any other systemic disease other than COPD and having vitamin B12 or folic acid deficiency were also excluded from the study. A detailed clinical history of respiratory symptoms was also obtained. Chest X-ray, spirometry, and routine blood investigations were done in all patients. Dyspnea was measured by the mMRC Dyspnea scale in both the groups for assessing the health status of a patient and grading the degree of a patient's breathlessness and disability caused.

### Statistical Analysis

GraphPad PRISM version 6.01 (GraphPad Software Inc., La Jolla, CA, USA) was used for the analysis of data. All demographic and clinical data were expressed as a mean ± standard deviation (SD) or percentage. The Chi-square test was used for categorical data, and groups were compared by unpaired *t*-test or one-way analysis of variance. $p < 0.05$ was considered statistically significant.

## Results

In this study, we had taken 250 stable COPD patients representing all stages of disease severity as defined by GOLD who were recruited.

The baseline characteristics of the study groups are shown in Table 1. As per the WHO criteria for patients to be anemic in our study, we found 62 patients in the anemic group while 188 patients in nonanemic group. The prevalence of anemia in COPD patients in the present study was 24.80%. Majority of patients were male in both the groups, and the proportions of males were slightly higher in the nonanemic group as compared with the anemic group. The mean hemoglobin levels in the anemic group were 10.6 ± 1.3 gm/dL, whereas in the nonanemic group, it was 14.2 ± 1.4 gm/dL. Difference in body mass index (BMI) of anemic (19.83 ± 4.06) and nonanemic (24.45 ± 4.51) groups was found to be significant with a *p*-value < 0.001. The age of the patients ranged from 35 to 75 years. The mean age of anemic COPD patients was slightly higher than nonanemic COPD patients. The smoking status of anemic patients was higher as compared with nonanemic patients in COPD with a statistically significant *p*-value < 0.001. Mean values of spirometric variables of anemic groups of post FEV1% pred (44.73 ± 18.82), post FVC % (59.70 ± 1.45), and post FEV1/FVC (55.06 ± 9.53) were lower when compared with nonanemic group of COPD patients, i.e., FEV1 % pred (59.95 ± 7.73), post FVC % (64.73 ± 0.96), and post FEV1/FVC (60.35 ± 7.09), and were significantly higher with *p*-value < 0.001.

Table 2 shows that SF36 score of patients of nonanemic (53.98 ± 5.71) was found to be statistically significantly higher ($p = 0.001$) as compared to that of anemic (39.13 ± 4.66). Higher SF36 score was indicative of better QOL.

In Figure 1, proportions of male (85.63%) patients were more anemic as compared with nonanemic (77.41%) male patients, there was more number of smokers (79.03%) in anemic patients as compared with nonanemic smokers (66.48%) in a total of COPD patients.

In Figure 2, the proportion of anemic patients was found to be higher in grade III (50%) than nonanemic mMRC grade III and IV, while the proportion of nonanemic patients was higher in mMRC grade I (41.48%) and II (28.19%). The difference in mMRC grade of patients of anemic and nonanemic groups was found to be statistically significant ($p = 0.04$). The difference in mMRC grade of patients of anemic and nonanemic was found to be statistically highly significant.

**Table 1:** Distribution of demographic data and statistic analysis of the anemic and nonanemic groups in COPD patients with regard to age, gender, height, weight, BMI, smoking status, Hb, and spirometry parameters

| *S. No.* | | *Anemic (n = 62) Mean ± SD* | *Non-anemic (n = 188) Mean ± SD* | *p-value* |
|---|---|---|---|---|
| | | *Demographic data* | | |
| 1 | Age (years) | 57.98 ± 11.97 | 52.34 ± 11.63 | <0.002 |
| 2 | Height (cm) | 161.97 ± 9.65 | 160.54 ± 8.77 | 0.583 |
| 3 | Weight (kg) | 63.45 ± 13.58 | 51.98 ± 12.41 | <0.001* |
| 4 | BMI (kg/m$^2$) | 19.45 ± 4.51 | 24.83 ± 4.06 | <0.001* |
| | | *Hematologic parameters* | | |
| 5 | Hb (gm/dL) | 10.6 ± 1.3 | 14.2 ± 1.4 | <0.001* |
| 6 | MCV (fl) | 86.0 ± 9.2 | 86.8 ± 10.7 | <0.001* |
| 7 | MCH (pg/mL) | 28.7 ± 2.6 | 31.3 ± 9.2 | <0.001* |
| 8 | MCHC (gm/dL) | 32.5 ± 1.0 | 33.0 ± 1.5 | <0.001* |
| 9 | Platelets (109/L) | 278 ± 70 | 249 ± 56 | <0.001* |
| 10 | RBC (106/µL) | 3.7 ± 0.5 | 4.8 ± 0.6 | <0.001* |
| 11 | Pack per year) | 32.69 ± 9.26 | 18.74 ± 15.21 | <0.001* |
| 12 | Post FVC % | 59.70 ± 1.45 | 64.73 ± 0.96 | <0.001* |
| 13 | Post FEV1/FVC (%) | 55.06 ± 9.53 | 60.35 ± 7.09 | <0.001* |
| 14 | Post FEV1 % predicted | 44.73 ± 18.82 | 59.95 ± 7.73 | <0.001* |

**Table 2:** Distribution of study population according to SF36 score

| *Group* | *No. of patients* | *Min.* | *Max.* | *Median* | *Mean* | *SD* |
|---|---|---|---|---|---|---|
| Anemic | 62 | 31.00 | 46.00 | 41.00 | 39.13 | 4.66 |
| Nonanemic | 188 | 43.00 | 65.00 | 54.00 | 53.98 | 5.71 |
| Total | 250 | 31.00 | 65.00 | 51.00 | 50.07 | 8.53 |

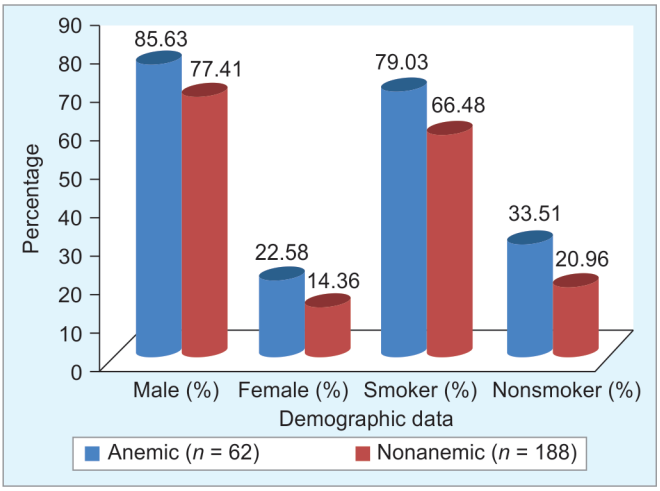


**Fig. 1:** Demographic profile of anemic and nonanemic study subjects with respect to gender and smoking status

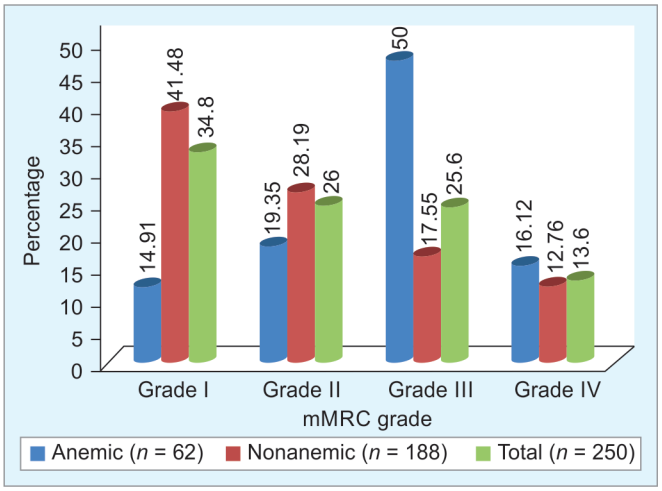


**Fig. 2:** Distribution of study population according to mMRC grade in anemic and nonanemic groups in COPD patients

In Figure 3, according to the GOLD criteria, COPD patients were grouped into four stages based on their severity in both the COPD groups. The proportion of anemic patients was higher in stage III (50%) and IV (23%) when compared with nonanemic patients of stage III (48 %) and IV (19%) of COPD groups with significant ($p$-value = 0.03). Mean values of spirometric variables such as FEV1 % pred, FVC %, and FEV1/FVC were lower in anemic patients in comparison with nonanemic COPD patients. Patients with anemia had severe COPD.

In Figure 4, 6-minute walk distance (6MWD) test was significantly lower in anemic patients (267.9 ± 86.7) when compared with nonanemic patients (373.0 ± 122.8) with significant $p$-value < 0.001,

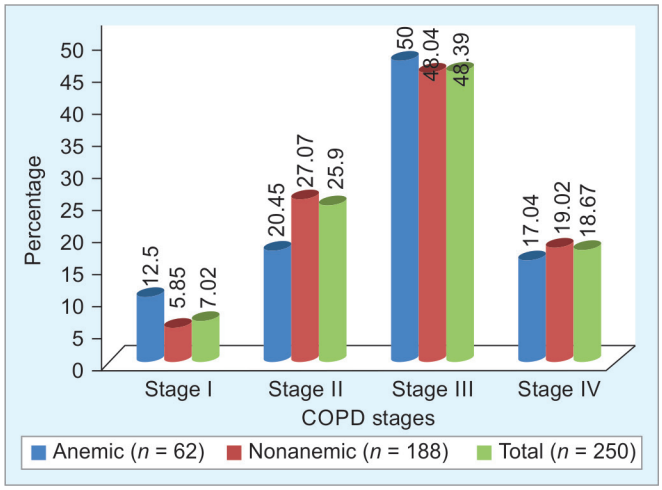


**Fig. 3:** Distribution of study population according to stage of COPD anemic and nonanemic groups in COPD patients

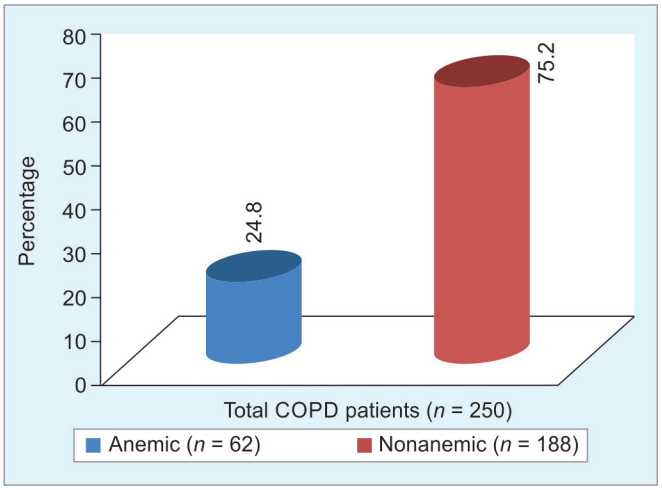


**Fig. 5:** Prevalence of anemia among COPD (*n* = 88) population anemic and nonanemic (*n* = 410) groups in COPD patients

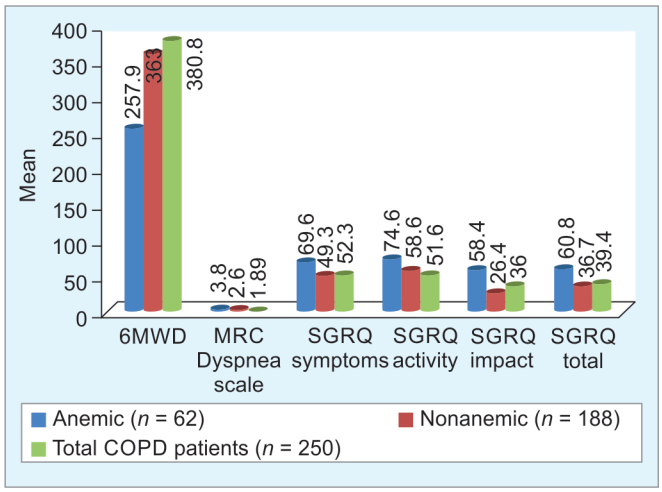


**Fig. 4:** 6MWD, degree of dyspnea, and quality of life in COPD patients, divided according to the presence of anemia

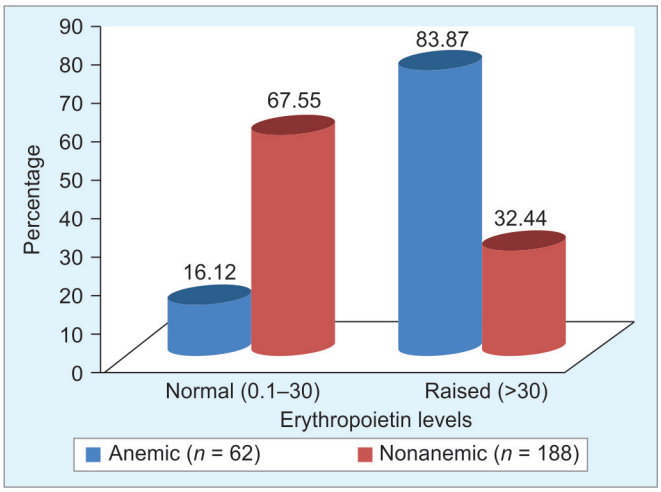


**Fig 6:** Distribution of study population according to erythropoietin levels

dyspnea scale and QOL according to the presence or absence of anemia are reported in Figure 3. Mean MRC values were significantly higher (3.8 ± 1.1 vs 2.6 ± 1.3, $p = 0.002$) in anemic compared with nonanemic patients. Quality of life, measured by using the SGRQ questionnaire, was significantly worse in subjects with anemia, as far as total score or symptoms, activity, or impact scores were concerned.

Figure 5 shows prevalence of anemia among COPD patients. Anemia was defined as hemoglobin level of <13 gm/dL among males and <12 gm/dL among females. Prevalence of anemia in COPD = 24.8%. Out of 250 patients of COPD, hemoglobin levels of 62 (24.8%) were found to be below normal levels and were diagnosed as anemic and classified as anemia in the present study, while hemoglobin levels of the rest 188 (75.2%) patients were found to be normal and were classified as nonanemic. Prevalence of anemia in COPD = 24.8%.

Figure 6 shows erythropoietin levels of majority of patients of anemia (83.87%) were found to be raised, while majority of patients of nonanemic (67.55%) had normal erythropoietin levels. The difference in erythropoietin levels of anemia and nonanemic was found to be statistically significant ($p = 0.027$).

## Discussion

Over the period of last 10 years, various studies have demonstrated the prevalence of anemia in COPD patients and several pathogenic mechanisms have been proposed explaining anemia in COPD patients. To the best of our knowledge, this is the first study that evaluated the long-term effect of anemia on COPD survival in the general population. Our data showed that the prevalence of anemia in COPD was 24.87% and that anemia was associated with increased long-term mortality. Hemoglobin level was well-correlated with mortality. Even a mild decrease in hemoglobin increased the risk of death, and the risk of mortality increased in proportion to the decrease in hemoglobin. This difference in the prevalence rate can be due to various factors, such as type of studies, COPD patients in the study (either stable or exacerbated or admitted patients), the use of different cutoff levels of hemoglobin to define anemia, or the existence of different confounding factors such as the presence of other known causes of anemia, such as heart failure and renal failure.

The prevalence of anemia in COPD patients has been reported to vary from 7.5 to 33%. Many retrospective studies have been

done, which related anemia pathogenetically to the presence of inflammation.[6] Erythropoiesis in COPD can be affected by various factors and it can manifest by either anemia or polycythemia, development of anemia or polycythemia depends on the balance between inflammatory stimuli and hypoxic stimuli.[7] The mechanism of anemia in COPD is probably multifactorial. There may be anemia of chronic disease related to inflammation, iron and vitamin deficiency, comorbidities, hypogonadism, or treatment-related.[8]

We found the prevalence of anemia in COPD patients to be 24.87%. Pulmonary function variables (FEV1, FVC, and FEV1/FVC) were lower in anemic patients in comparison with nonanemic COPD patients with significant difference, and we do find that patients with anemia had more severe COPD in terms of the post-bronchodilator FEV1%, which was in accordance to the study by Boutou et al.[9] In a previous cross-sectional study by Zavarreh et al.,[10] in 760 COPD patients, they found no correlation between severity of COPD and anemia, but they found anemic patients (71.1 ± 8.5) to be significantly older than nonanemic patients (65.4 ± 12.8) ($p = 0.03$). Shorr et al. in a retrospective data analysis of 2404 COPD patients from the United States also reported a very high frequency of anemia in COPD patients of 33%, which was almost comparable to our study.[11–13]

In patients with COPD and chronic respiratory failure, higher hemoglobin level was associated with longer survival. In a prospective study of stable COPD outpatients, anemia was present in 62 (24.87%) patients and these patients showed a significantly higher mMRC score, lower 6MWD, and shorter median survival (49 vs 74 months) than nonanemic patients. Anemia was significantly associated with increased dyspnea in our study, which was assessed by mMRC grade ($p = 0.04$). We also found association between worsening of dyspnea (calculated as per mMRC score) with anemia as 50% of anemic patients having mMRC dyspnea grade III and IV. In nonanemic patients, only 17% were of mMRC dyspnea grade III and IV. The proportion of anemic patients was found to be higher in grade III (50%) than nonanemic of mMRC grade III and IV, while the proportion of nonanemic patients was higher of mMRC grade I (41.48%) and II (28.19%). Difference in mMRC grade of patients of anemic and nonanemic groups was found to be statistically significant ($p = 0.04$). Difference in mMRC grade of patients of anemia and nonanemic was found to be statistically highly significant.

Chronic COPD has a greater role in initiation of anemia than a severe COPD. However, several studies stated that anemia can be induced by extensive inflammation following COPD or failure in response toward the erythropoietin, but this hypothesis needs to be backed by more evidences. Dysfunction in transportation of the iron reticulo-endothelial resources can cause anemia in COPD patients.[14]

The proportion of anemic patients was higher in stage III (50%) and IV (23%) when compared with nonanemic patients of stage III (48 %) and IV (19%) of COPD groups ($p = 0.03$). Mean values of spirometric variables such as FEV1% pred, FVC%, and FEV1/FVC were lower in anemic patients in comparison with non-anemic COPD patients. Patients with anemia had severe COPD. Mean FEV1% predicted in our studied patient was 32.53% in anemic patients, while it was 41.4% in nonanemic patients which is in accordance with the study conducted by Krishnan,[15] where mean FEV1% of predicted was 43.17% and 42.07% in anemic and nonanemic patients, respectively. Most of our studied patients were in GOLD stage III and IV, whereas majority of patients were in GOLD stage III in another study by Mathias John. There was no correlation between lung function test and anemia. Similar results have been shown in the studies conducted by Silverberg et al.[16]

The frequency of anemia in our study was 24.87% which is similar to frequency of 21% by Michael Halpern and 23% by John Mathias.[17,18] There was no significant difference in frequency of anemia with respect to gender consistent with other studies by El-Korashy et al.[19] The frequency of polycythemia (hemoglobin ≥ 17 gm/dL in males and ≥15 gm/dL in females) was 5.2%, which is similar to the study by Cote[20] (6%).

Out of 15 anemic patients, 13 (86.66%) patients had normocytic normochromic type of anemia, whereas 2 (13.33%) had microcytic hypochromic type of anemia. Although no study on iron profile in anemic COPD patients was available for comparison, the results are consistent with iron profile in anemia of chronic disease in studies by Casanova et al.[21] Erythropoietin levels were significantly raised in anemic patients (83.87%) while majority of nonanemic patients (67.55%) had normal erythropoietin levels. Similar results have been shown in another study by Mathias John. The clinical parameter which had significant correlation with anemia in our study were number of exacerbations of COPD leading to hospitalization; similar results have been seen in studies conducted by Cote. Mean (SD) BMI of our study population was 20.01 (4.15) kg/m$^2$ in anemic and 19.72 (3.97) kg/m$^2$ in nonanemic patients which is similar to the study by Mathias John where mean (SD) BMI of 23.8 (1.7) kg/m$^2$ and 23.2 (0.6) kg/m$^2$ were observed in anemic and nonanemic patients, respectively.

Anemia was independently associated with reduced exercise capacity as measured by 6MWD. The proportion of patients were higher in nonanemic group who completed > 300 m distance; which is in accordance with the study conducted by Cote.

Anemia was independently associated with increased dyspnea that was assessed subjectively by the mMRC scale. The proportion of patients of anemia (anemic) was found to be higher than that of nonanemic (nonanemic) having mMRC grade III (50.00% vs 17.55%). The difference in mMRC grade of patients of anemia and nonanemic was found to be statistically highly significant, which is in accordance to the study by Cote.

The Short Form-36 (SF-36) score of patients of nonanemic (nonanemic) (53.98 ± 5.71) was found to be statistically higher ($p = 0.001$) as compared with, anemia (anemic) (39.13 ± 4.66), which indicates poor quality of life in anemic patients, this was in accordance with the study conducted by Gokul Krishnan.

Fifty-seven patients (48 males and 14 females) with a mean (SD) age of 57.98 (11.96) years having COPD diagnosed by GOLD criteria were evaluated for frequency of anemia. In addition to baseline investigations, erythropoietin levels were done in a subgroup of studied patients. A total of 62 cases of anemia were detected giving a frequency of 24.84%. Majority of patients were in GOLD stage III and IV with a mean FEV1 32.53% of the predicted in anemic COPD patients.

These results are consistent with the findings of others who treated anemia in COPD with either anabolic steroids or blood transfusions. The study involving the use of anabolic steroids in COPD showed that the improvement in the Hb that was found was associated with an improvement in pulmonary function as judged by maximal inspiratory mouth pressure and peak workload.[22] In another study, transfusion of a mean of 2.2 units of packed cells in 10 anemic COPD patients in an intensive care unit was shown to lead to a significant reduction of both minute ventilation and work of breathing.[23] In a second study by the same group, blood transfusions allowed five anemic COPD patients, in whom trials

of weaning from a respirator before the transfusions had been unsuccessful, to be successfully weaned after the transfusions. All these studies, in addition to the present study, suggest that correction of the anemia in COPD.[24]

The various factors significantly associated with anemia in our study were number of exacerbations of COPD leading to hospitalization, BMI, erythropoietin levels, 6MWD, and quality of life. Anemia in patients with COPD is likely due to a combination of several factors. Elevated cytokines levels, especially tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-6 (IL-6). Moreover, persistent inflammation may be associated with poor clinical outcome for COPD patients.[25]

## Conclusion

Anemia reflects chronic illness and burden of disease, and our cohort included a relatively healthy population who regularly underwent the national health screening examination. The patients included in this study were newly diagnosed patients with COPD and probably milder than other cohorts previously reported. Therefore, the prevalence in our study might be lower than in other studies. Interestingly, other studies on stable outpatients with COPD have reported a prevalence of anemia ranging from 15.6% to 17.1%.

In conclusion, anemia occurs frequently in patients of COPD and is associated with poor quality of life and increased morbidity in the form of number of exacerbations and hospital admissions. Correcting anemia in these patients may improve their clinical outcome.

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