

## Chronic Obstructive Pulmonary Disease with Anemia as Comorbidity in North Indian Population

### Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is an increasing cause of morbidity and mortality worldwide. Anemia is seen as a common comorbidity in COPD patients associated with reduced functional capacity, impaired quality of life, greater likelihood of hospitalization, and early mortality. The aim is to study the prevalence of anemia in patients with COPD and to study its association with different parameters. **Materials and Methods:** In the present case-control study, 150 stable COPD patients were enrolled from the Outpatient Department of Respiratory Medicine, King George Medical University, Lucknow, from October 2015 to January 2017. GraphPad PRISM version 6.01 was used for the analysis of data. Chi-square test was used to compare between the groups.  $P < 0.05$  was considered statistically significant. **Results:** The present study showed the prevalence of anemia in COPD patients to be 31.6%. The mean hemoglobin level in anemic group was  $11.04 \pm 1.1$  g/dl, whereas in nonanemic group, it was  $13.9 \pm 0.8$  g/dl. Anemia was significantly associated with increased dyspnea in our study which was assessed by modified Medical Research Council grade ( $P = 0.04$ ). **Conclusion:** The prevalence of anemia in COPD patients was 31.6%. Anemia is present as comorbidity in COPD patients and is associated with poor quality of life and increased morbidity in the form of number of exacerbation and hospital admission. Identification and correction of anemia in COPD patients may improve their clinical outcome.

**Keywords:** Anemia, chronic obstructive pulmonary disease, hemoglobin

### Introduction

Chronic obstructive pulmonary disease (COPD), a chronic inflammatory disease, is a major worldwide health problem. According to the World Health Organization (WHO), 65 million people have moderate-to-severe COPD.<sup>[1]</sup> Crude estimates suggest that there are 30 million COPD patients in India, and it contributes to a significant and growing percentage of COPD mortality.<sup>[2]</sup>

Smoking and biomass exposure, along with genetic predisposition, are the major risk factors for developing COPD. Comorbidities are important events in the natural history of the disease and have a negative effect on the morbidity and mortality of COPD patients. Diabetes, hypertension, cardiovascular diseases, lung cancer, osteoporosis, and depression are common comorbidities seen in COPD patients.

Anemia is seen to be present as comorbidity in various chronic disease states, and

therefore, understanding its pathogenesis is important. In recent years, anemia is also seen as a common comorbidity in COPD patients and associated with reduced functional capacity, impaired quality of life, greater likelihood of hospitalization, and early mortality.<sup>[3]</sup> Thus, developing new tools for its treatment should be our priority.

Anemia of chronic disease (ACD) is an immune-driven abnormality associated with chronically very low levels of circulating hemoglobin that has been seen to occur in many inflammatory diseases. The systemic inflammation that is now recognized as a feature of COPD makes it a possible cause of ACD. If present in COPD, anemia could worsen dyspnea and limit exercise tolerance.<sup>[4]</sup>

Hemoglobin is the principal oxygen transport molecule. As per the WHO, men with hemoglobin levels  $<13$  g/dl and women with hemoglobin levels  $<12$  g/dl are defined as anemic.<sup>[5]</sup> Any decrease in hemoglobin levels results in a corresponding reduction

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in the oxygen-carrying capacity of the blood. Impairment of this mechanism exerts a negative impact on clinical status.<sup>[6]</sup> The prevalence of anemia in patients with COPD varies from 7.5% to 33%,<sup>[3,7]</sup> and this variability might be due to various methods of studies, selection of patient group, and various definitions of anemia.<sup>[8]</sup> We conducted a study in North Indian COPD population to evaluate the prevalence of anemia and to study its association with various parameters.

## Materials and Methods

### Study population and selection of subjects

The present study was carried out in the Department of Respiratory Medicine, King George Medical University, Lucknow. The study was approved by the Institutional Ethical Committee. One hundred and fifty stable COPD patients were enrolled from the Outpatient Department of Respiratory Medicine from October 2015 to January 2017 after obtaining written informed consent from all the patients.

The diagnosis of COPD was based on pulmonary function test which was done in all patients. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, COPD was defined on the basis of the postbronchodilator 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 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.<sup>[8]</sup>

1. GOLD stage 1 – mild: FEV1 ≥80% predicted
2. GOLD stage 2 – moderate: 50% ≤FEV1 <80% predicted
3. GOLD stage 3 – severe: 30% ≤FEV1 <50% predicted
4. GOLD stage 4 – very severe: FEV1 <30% predicted.

Anemia was defined according to the WHO criteria as hemoglobin level <13 g/dl in men and 12 g/dl in women. COPD patients were divided into two groups: anemic (Group 1) and nonanemic (Group 2) 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 modified Medical Research Council (mMRC) Dyspnea scale in both the groups for assessing 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 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, 150 COPD patients representing all stages of disease severity as defined by GOLD 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 47 patients in anemic group while 103 patients in nonanemic group. The prevalence of anemia in COPD patients in the present study was 31.6%. Majority of patients were male in both the groups and proportions of males were slightly higher in nonanemic group as compared to the anemic group. The mean hemoglobin levels in anemic group were 11.04 ± 1.1 g/dl, whereas in nonanemic group, it was 13.9 ± 0.8 g/dl. Difference in body mass index (BMI) of anemic and nonanemic group was not found to be significant although mean BMI of anemic patients was lower than nonanemic. The age of the patients ranged from 35 to 75 years. Mean age of anemic COPD patients was slightly higher than nonanemic COPD patients.

There was a positive correlation of hemoglobin with FEV1% predicted (FEV1% pred, *r* = 0.36) and negative correlation with age (*r* = -0.02, *P* = 0.87) and BMI (*r* = 0.03, *P* = 0.8).

Proportions of anemic patients were higher in age group of 51–60 and 61–70 years in comparison to nonanemic patients which were higher in age group of 41–50 years [Figure 1].

**Table 1: Demographic profile and spirometry variables of anemic and nonanemic chronic obstructive pulmonary disease patients**

Parameters	Anemic (n=47)	Nonanemic (n=103)	<i>P</i>
Age (years)	57.2±9.5	56.7±9.33	0.74
Height (cm)	159.40±7.87	158.85±7.25	0.67
Weight (kg)	52.38±9.88	51.71±11.6	0.73
BMI (kg/m <sup>2</sup> )	19.99±3.87	20.9±4.23	0.21
Male (%)	36 (76.6)	84 (81.5)	0.48
Female (%)	11 (23.4)	19 (18.4)	
FVC %	60.65±13.28	63.26±18.47	0.57
FEV1% predicted	40.25±11.6	45.18±15.9	0.059
Post FEV1/FVC	52.77±10.6	56.07±9.84	0.06
Hb (g/dl)	11.04±1.1	13.9±0.8	<0.0001

Data are presented as mean±SD or percentages depending on the distribution. *P*<0.05 was considered statistically significant. FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 s, BMI: Body mass index, Hb: Hemoglobin

In anemic group, large number of patients was in age group of 61–70 years followed by 51–60 years.

According to the GOLD criteria, COPD patients were grouped into four stages based on their severity in both the COPD groups [Figure 2]. Proportion of anemic patients was higher in Stage 3 and 4 (82%) while proportions of nonanemic patients were (65%) ( $P = 0.03$ ). Mean values of spirometric variables such as FEV1% pred, FVC %, and FEV1/FVC were lower in anemic patients in comparison to nonanemic COPD patients. Patients with anemia had severer COPD.

Proportion of anemic patients was found to be higher (45%) than nonanemic of mMRC Grade 3 and 4, while proportion of nonanemic patients was higher of mMRC Grade 1 and 2 (77%) [Figure 3]. Difference in mMRC grade of patients of anemic and nonanemic group was found to be statistically significant ( $P = 0.04$ ).

### Discussion

Anemia is one of the extrapulmonary manifestations of COPD. The prevalence of anemia has been reported between 7.5% and 33%.<sup>[3,7]</sup> John *et al.*<sup>[9]</sup> in 2006 reported the prevalence of anemia in COPD patients to be 23.1%, while another study observed anemia in 13% of 101 COPD patients and they pathogenetically related it to the presence of inflammation.<sup>[10]</sup> Halpern *et al.*<sup>[11]</sup> found anemia in 21% of total patients with a COPD diagnosis while Parveen *et al.*<sup>[12]</sup> in a hospital-based, cross-sectional study in 200 COPD patients reported anemia in 18% of the patients. Of 107 consecutive patients hospitalized with an acute exacerbation of COPD patients (AECOPD), 47 (43.9%) were found to be anemic on admission in a study by Silverberg *et al.*<sup>[13]</sup> One recent study by El-Korashy *et al.*<sup>[14]</sup> showed that almost half of patients have anemia; however, one earlier study reported a very low prevalence of anemia in COPD patients that is 6%.<sup>[15]</sup>

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. Shorr *et al.* in a retrospective data analysis of 2404 COPD patients from the USA also reported a very high frequency of anemia in COPD patients of 33%,<sup>[16]</sup> which was comparable to our study.

We found the prevalence of anemia in COPD patients to be 31.6%. Pulmonary function variables (FEV1, FVC, and FEV1/FVC) were lower in anemic patients in comparison to nonanemic COPD patients although difference was not significant, but we do find that patients with anemia had more severe COPD in terms of the postbronchodilator FEV1%, which was in accordance to the study by

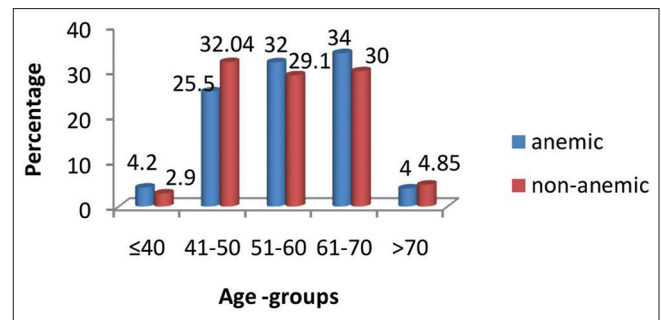


Figure 1: Distribution of anemic and nonanemic chronic obstructive pulmonary disease patients according to different age groups

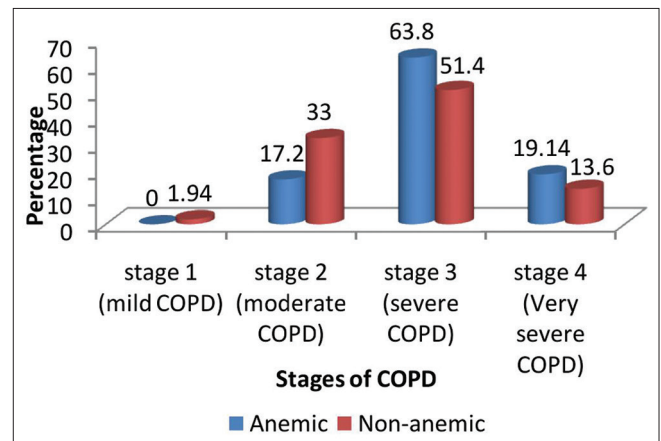


Figure 2: Comparison of anemic and nonanemic chronic obstructive pulmonary disease patients according to stages of chronic obstructive pulmonary disease. Chi-square test was used for analysis of data.  $P < 0.05$  was considered statistically significant. Stage 1 and 2 versus Stage 3 and 4 ( $P = 0.03$ )

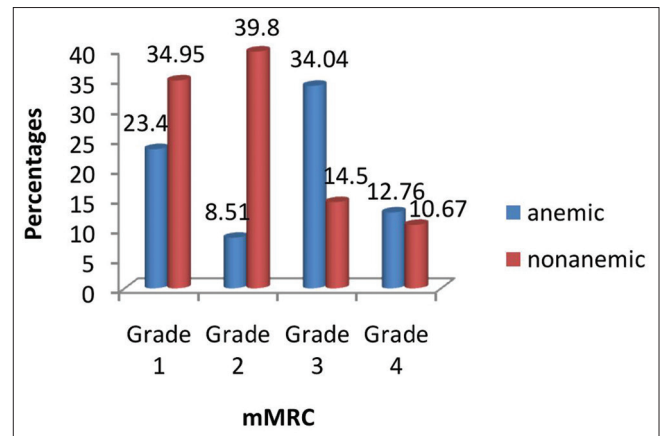


Figure 3: Distribution of anemic and nonanemic chronic obstructive pulmonary disease patients according to modified Medical Research Council grade. Chi-square test was used for the analysis of data.  $P < 0.05$  was considered statistically significant on comparison of groups on the basis of modified Medical Research Council grade ( $P = 0.04$ )

Casanova *et al.*<sup>[15]</sup> In a previous cross-sectional study by Zavarreh *et al.*,<sup>[17]</sup> in 760 COPD patients, they found no correlation between severity of COPD and anemia, but they found anemic patients ( $71.1 \pm 8.5$ ) to be significantly older than nonanemic patients ( $65.4 \pm 12.8$ ) ( $P = 0.03$ ).

Likewise, in our study, the anemic patients were older than nonanemic and proportion of anemic patient was more in higher age group (61–70). Therefore, we suggest that hemoglobin levels estimation should necessarily be done in older age group. Proportion of anemic patients was higher in Stage 3 and 4 which were also observed in a study by Parveen *et al.*<sup>[10]</sup> We also found anemia to be associated with increased morbidity in the form of number of exacerbation and hospital admissions. Ferrari *et al.* associated anemia with increase of dyspnea and deterioration in a health-related quality of life.<sup>[18]</sup> In patients with COPD and chronic respiratory failure, higher hemoglobin level was associated with longer survival.<sup>[19]</sup> In a cohort study of 5683 stable COPD outpatients, anemia was present in 116 (17%) patients, and these patients showed a significantly higher mMRC score, lower 6-min walk distance, and shorter median survival (49 vs. 74 months) than nonanemic patients.<sup>[20]</sup> 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 45% of anemic patients having mMRC dyspnea Grade 3 and 4. In nonanemic patients, only 27% were of mMRC dyspnea Grade 3 and 4.

Multiple independent factors have been associated with increased risk of readmission in persons with COPD, and among them, anemia was one of the greatest risks; anemic patients had a 25% higher risk of readmission than nonanemic patients.<sup>[21]</sup> We also found in our study that exacerbations leading to hospitalization were more in anemic patients in comparison to nonanemic in the previous year. A study on 117 AECOPD also showed that anemia (Hb <13 g/dl) and previous exacerbations (3.5 exacerbations) were independent predictors of mortality after 1 year in patients hospitalized for AECOPD.<sup>[22]</sup> Dyspnea and fatigue are important symptoms in COPD, and both symptoms have a negative impact on the quality of life of COPD patients. A case series of five ventilator-dependent COPD patients with anemia showed that whole-blood transfusion and raising the hemoglobin levels to >12 g/dl resulted in successfully weaning all the patients.<sup>[23]</sup> All these studies show that anemia when present in COPD patients have a definitive impact on the quality of life of COPD patients. Therefore, correction of anemia in COPD patients may improve their clinical outcome. Anemia is increasingly recognized as an important comorbidity in COPD, affecting a relevant number of patients with high indices of mortality, increased health-care costs, and having a negative impact on quality of life. Previous studies have shown that anemia is associated with an increased risk of hospitalization and mortality in patients with COPD. Therefore, it is important to study both conditions together to improve patient management and survival. Hence, efforts should be made to prevent, diagnose, and treat anemia as early as possible in COPD patients as a means

of improving their overall prognosis, reducing the increase in hospitalizations, reducing respective length of stay, and thereby improving their health-related quality of life in patients with COPD.

## Conclusion

COPD is a multicomponent disease which affects the physiological conditions and social life of patients. The prevalence of anemia in COPD patients was 31.6%, and we found that proportion of anemic patients were higher in Stage 3 and 4 and had more dyspnea. Anemia is present as comorbidity in COPD patients and is associated with poor quality of life and increased morbidity in the form of number of exacerbation and hospital admission. During severe COPD exacerbations, anemia can be a risk factor for mortality. The clinical impact of anemia is significant, so correction of anemia should be an important goal in the management of COPD.

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## Conflicts of interest

There are no conflicts of interest.

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