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ANEMIA IN COPD: PREVALENCE, ASSOCIATION WITH DISEASE SEVERITY AND QUALITY OF LIFE

Respiratory Medicine

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is commonly linked to polycythemia, but systemic inflammation—a key feature of COPD—may also lead to anemia of chronic disease (ACD). Recent evidence suggests that anemia may be more prevalent in COPD than previously thought, affecting around 11% to 20% of patients. Despite its recognized impact in conditions like chronic heart failure and renal insufficiency, anemia has not been extensively studied in COPD. This study evaluated 100 patients (79 males and 21 females) with confirmed COPD through spirometry to assess the prevalence of anemia. Along with routine tests, erythropoietin and hepcidin levels were measured, and patients' morbidity was analyzed using the modified Medical Research Council (mMRC) dyspnea scale and COPD Assessment Test (CAT) score. Anemia was detected in 19 patients (18 males and 1 female), representing a 19% prevalence. Most cases (15 out of 19) were normocytic normochromic, while 4 exhibited normocytic hypochromic anemia. These anemic patients, predominantly in GOLD stage III, demonstrated lower serum iron, transferrin saturation, and total iron-binding capacity (TIBC). Erythropoietin levels were significantly higher in anemic patients, while hepcidin levels were notably lower compared to non-anemic individuals. The correlation between CAT scores, mMRC grades, and anemia highlighted that disease severity worsens with progression, further diminishing quality of life, especially in anemic patients.

KEYWORDS

pulmonology, hematology, anemia, erythropoetin, COPD

INTRODUCTION

Chronic inflammatory lung disease, or chronic obstructive pulmonary disease (COPD), is defined by a gradual and non-reversible reduction in airflow. Fibrosis, mucus, and cell hyperplasia or accumulation constrict the small airways. Clinically, COPD becomes apparent only after prolonged restriction or obstruction of the airways. The primary factor in the pathophysiology of COPD is an excessive inflammatory response of the lungs to harmful inhaled gases or particles, such as secondhand smoke, cigarette smoke, biomass exposure, air pollution, chemicals, dust, fumes, and Alpha-1 deficiency (Pauwels et al., 2001). Key indicators and symptoms of COPD include shortness of breath, wheezing, chest tightness, persistent cough, sputum production, respiratory infections, low energy, inadvertent weight loss, and swelling in the ankles, feet, or legs.

It is commonly known that anemia coexists with chronic conditions such as cancer, inflammatory diseases, heart failure, and viral infections. COPD-related inflammation is often associated with significant extra-pulmonary systemic effects, including exercise limitation, skeletal muscle dysfunction, weight loss, osteoporosis, and anemia (Agusti et al., 2003). As a result, anemia is thought to be a prevalent comorbidity in COPD patients, associated with lower quality of life, higher risk of hospitalization, earlier death, and decreased functional capacity (Sarkar et al., 2015).

Numerous studies and publications have shown that anemic COPD patients have significantly higher erythropoietin (EPO) levels than non-anemic patients, suggesting that anemic COPD patients may have increased EPO resistance (Rk & S, 2016). To control iron homeostasis, the hormone hepcidin interacts with the transmembrane iron export protein ferroportin as a counter-regulator of iron absorption and recycling (Weiss & Goodnough, 2005). Anemia associated with chronic obstructive pulmonary disease is often normocytic and normochromic, although it can sometimes become microcytic and hypochromic as the illness worsens (Schols et al., 1996).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies airflow limitation in COPD into four stages. Patients with COPD can have their illness severity and quality of life assessed more effectively by using the COPD Assessment Test (CAT) score and the Modified Medical Research Council (mMRC) questionnaire, along with GOLD criteria. This approach takes a comprehensive look at the disease's progression, severity, and impact on quality of life.

Numerous studies have demonstrated significant correlations between the incidence of anemia and COPD, as well as the relationships between EPO, hepcidin, and C-reactive protein levels. Analyzing these correlations can help us better understand the relationship between anemia and COPD. Furthermore, a deeper understanding of its correlation with disease severity and quality of life will be possible through the correlation of these data with clinical evaluation utilizing the CAT score and mMRC score. Depending on positive study results, the identification and correction of anemia in COPD patients may improve their clinical outcomes.

MATERIAL AND METHODS

The study was conducted in the Department of Medicine, Respiratory Medicine, and Biochemistry at ABVIMS & Dr. RML Hospital in New Delhi. This observational cross-sectional study spanned approximately 17 months, from January 1, 2021, to May 30, 2022. During this period, a total of 100 patients with COPD were recruited from the Medicine and Respiratory Medicine outpatient department and emergency services after meeting the established inclusion and exclusion criteria.

The sample size was calculated using a prevalence of anemia in COPD patients of 43.9%, as reported by Silverberg et al. (Silverberg et al., 2014). With a 95% confidence level and a relative error of 20%, the estimated sample size was 123. Despite the calculated sample size, a convenient sample size of 100 was taken due to the lower number of eligible patients reporting during the study period.

All participants provided informed consent prior to their inclusion in the study. Patients were fully briefed about the study objectives, procedures, and potential risks in their native language. Bilingual consent forms were used to ensure comprehension. Participation was voluntary, and patients were free to withdraw from the study at any time without affecting their medical care.

The study included all adult patients presenting to the Medicine and Respiratory Medicine outpatient departments (OPD). Only those patients who were diagnosed with COPD based on the GOLD criteria were eligible for participation.

Patients were excluded if they had any chronic diseases such as chronic kidney disease (CKD), chronic liver disease (CLD), congestive cardiac failure (CCF), interstitial lung disease (ILD), or autoimmune disorders. Additionally, patients with chronic infections, including pulmonary tuberculosis or HIV, were not considered for the study. Pregnant and lactating women were also excluded. Furthermore, individuals diagnosed with malignancies or undergoing chemotherapy, as well as those with bleeding disorders, were not eligible to participate.

A total of 100 COPD patients who met the inclusion criteria were subjected to a comprehensive evaluation. This included a detailed history covering age, sex, body weight, and the presence of any comorbidities. A thorough clinical examination was also performed, focusing on respiratory symptoms and systemic manifestations.

Standardized laboratory tests were conducted in the pathology, microbiology, and biochemistry departments of the hospital. These investigations included:

Complete blood count (CBC) including hemoglobin (HB), white blood cell (WBC) count, differential leukocyte count (DLC), platelet count, red blood cell (RBC) count, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, and erythrocyte sedimentation rate (ESR)

- Peripheral blood analysis
- Kidney function tests (serum urea, creatinine, and uric acid)
- Liver function tests (total bilirubin, direct and indirect bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphatase)
- Iron profile (total iron, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), and transferrin saturation)
- Serum erythropoietin levels
- Vitamin B12 and folate levels
- Hepcidin levels
- C-reactive protein (CRP)

Pulmonary function tests (PFTs) were conducted using spirometry in the Department of Respiratory Medicine. The NDD Medizintechnik, Switzerland, Easy on-PC Software was used for the spirometry tests. PFT results were interpreted according to GOLD criteria, and patients were classified into different stages of COPD based on the severity of their airflow obstruction.

Statistical Analysis:
The clinical profile of the patients and study outcomes were documented in a Microsoft Excel spreadsheet. Data were analyzed and compared using standard statistical techniques in IBM SPSS version 22. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

A total of 100 patients (71 males and 29 females) with COPD, as documented by lung function tests and diagnosed using GOLD criteria, were evaluated for the frequency of anemia. In addition to baseline investigations, 19 cases of anemia were detected, giving a frequency of 19% (Table 1).

The mean age of the patients was 57.18 ± 10.67 years, with most anemic COPD patients being in the older age group. Out of the 19 anemic patients, 18 were males and 1 was female. Normocytic normochromic anemia was present in 15 patients (78.94%), while the remaining patients had normocytic hypochromic anemia.

Table 1: Haematological Finding In COPD Study Subjects (n=100)

Finding	Male	Female	Total
Anaemia	18 (25.4%)	1 (3.4%)	19 (19.0%)
Normal	43 (60.6%)	28 (96.6%)	71 (71.0%)
Polycythemia	10 (14.1%)	0	10 (10.0%)

The majority of anemic COPD patients were in GOLD Stage III (47.36%), followed by GOLD Stage II (36.84%). The severity of anemia was highest in COPD Stage III (Table 2). Most anemic patients had decreased serum iron levels, transferrin saturation, and total iron-binding capacity (TIBC).

Table 2: Association Of Anaemia With The Severity Of COPD (n=100)

Gold stage	COPD without anaemia (n=81)	COPD with anaemia (n=19)	Total
1	7 (100%)	0	7 (7.0%)
2	19 (73.1%)	7 (26.9%)	26 (26.0%)
3	33 (78.6%)	9 (21.4%)	42 (42.0%)
4	22 (88.0%)	3 (12.0%)	24 (24.0%)

The C-reactive protein (CRP) level was higher in COPD patients overall, with a mean CRP level of 3.13 ± 1.37 mg/dl (Table 4). Among anemic patients, the mean CRP level was 2.87 ± 0.97 mg/dl, while in non-anemic patients, it was 3.20 ± 1.45 mg/dl.

SpO2 levels were significantly lower in COPD patients with anemia (92.74 ± 1.09%) compared to non-anemic COPD patients (93.85 ± 1.55%).

Erythropoietin levels were elevated in all COPD patients, but significantly higher in anemic COPD patients compared to non-anemic patients. The hepcidin level in anemic COPD patients was 26.62 ± 3.31 ng/dl, whereas in non-anemic patients, it was 40.69 ± 8.87 ng/ml. This indicates that hepcidin levels were significantly lower in anemic COPD patients than in their non-anemic counterparts.

Table 3: Association Of Anaemia With mMRC Grade

mMRC grade	COPD without anaemia (n=81)	COPD with anaemia (n=19)	Total
0	5 (6.2%)	0	5 (5.0%)
1	11 (13.6%)	0	11 (11.0%)
2	24 (29.6%)	4 (21.1%)	28 (28.0%)
3	28 (34.6%)	13 (68.4%)	41 (41.0%)
4	13 (16.0%)	2 (10.5%)	15 (15.0%)

We found that in COPD subjects with anemia, CAT grading was high in 94.7% of patients and very high in 5.3%. In contrast, in COPD subjects without anemia, CAT grading was high in 53.1% and very high in 4.9%.

We also observed that patients' dyspnea worsened as the disease progressed, with higher GOLD stages correlating with more severe symptoms. The mMRC grade showed a direct correlation with GOLD staging (Table 3), indicating that disease severity increases with advanced stages of COPD.

DISCUSSION:

A total of 100 consecutive patients (71 males and 29 females) with COPD, as documented by lung function tests, were evaluated for the frequency of anemia. A total of 19 cases of anemia were detected. The mean age of patients was 57.18 ± 10.67 years, and the majority of anemic COPD patients were in the older age group. Similar findings were observed in studies by Cote C et al. (Cote et al., 2007), Parveen et al. (Parveen et al., 2014), and John M et al. (John et al., 2006), which are comparable to our study.

In our study, 47 of the 100 COPD patients were non-smokers, and 53 were smokers, which is lower than the findings of Cote C et al. (Cote et al., 2007) and Parveen et al. (Parveen et al., 2014), who reported 90% and 60% smokers, respectively. Both studies suggested that there was no significant difference in smoking habits between anemic and non-anemic patients, while our study found anemia to be significantly more prevalent in patients with a history of smoking.

The prevalence of anemia in our study was 19%, which is similar to the prevalence reported by C-Cote et al. (Cote et al., 2007) (17%), Michael Halpern et al. (Halpern et al., 2006) (21%), John Matthias et al. (John et al., 2005) (23%), and Parveen et al. (Parveen et al., 2014) (18%).

In our study, we found that CRP levels were higher in COPD patients, which is consistent with it being an important inflammatory marker in chronic inflammatory diseases like COPD. The mean CRP level was 3.13 ± 1.37 mg/dl (normal <1 mg/dl). In anemic patients, the mean CRP was 2.87 ± 0.97 mg/dl, and in non-anemic patients, it was 3.20 ± 1.45 mg/dl (P-value 0.34). These results are similar to the findings of Y

Zhang et al. (Zhang et al., 2012) and SE El-Deek et al. (El-Deek et al., 2013), who observed that serum CRP concentrations were significantly higher in COPD patients in GOLD stages III and IV compared to those in stages I or II.

While our study results align with these previous studies, there was no significant difference in CRP levels between anemic and non-anemic COPD patients. For the analysis of dyspnea, we used mMRC grades. Among the 81 non-anemic patients, 5 (6.2%) were in mMRC grade 0, 11 (13.6%) in mMRC grade 1, 24 (29.6%) in mMRC grade 2, 28 (34.6%) in mMRC grade 3, and 13 (16%) in mMRC grade 4. Among the 19 anemic COPD patients, 4 (21.1%) were in mMRC grade 2, 13 (68.4%) in mMRC grade 3, and 2 (10.5%) in mMRC grade 4 (P-value 0.06). There was no significant difference between the anemic and non-anemic groups regarding mMRC grading.

In the anemic COPD group, we assessed the severity of anemia using Hb levels. In the 9-10 gm/dl group (n=4), 3 (75%) were in mMRC grade 3, and 1 (25%) was in mMRC grade 4. In the 10-11 gm/dl group (n=6), 4 (66.7%) were in mMRC grade 3, 1 (16.7%) in mMRC grade 2, and 1 (16.7%) in mMRC grade 4. In the 11-12 gm/dl group (n=5), 3 (60%) were in mMRC grade 3, and 2 (40%) were in mMRC grade 2. In the 12-13 gm/dl group (n=4), 3 (75%) were in mMRC grade 3, and 1 (25%) in mMRC grade 2 (P-value 0.69), indicating no significant association between anemia severity and mMRC grading.

Our study observed that dyspnea worsened as COPD progressed to higher GOLD stages. The mMRC grade showed a direct correlation with GOLD staging, which is supported by the studies of Hayata A et al. (Minakata et al., 2016), Pitta et al. (Pitta et al., 2005), and Sakamoto et al. (Sakamoto et al., 2016). These studies, similar to ours, found that as the severity of COPD (GOLD stage) increases, dyspnea worsens, and physical activity is progressively restricted. We also noted that anemia is very common in COPD patients, and elevated serum CRP levels, decreased hepcidin levels, and increased erythropoietin levels may play a significant role in the etiopathogenesis of anemia in these patients. This has been thoroughly examined in our study.

In conclusion, our study highlights the correlation between CAT scores and mMRC grades with disease progression in COPD. The presence of anemia exacerbates the disease's impact on quality of life, as the severity of COPD increases with disease progression.

CONCLUSION:

100 patients (71 males and 29 females) with a mean (SD) age of 57.18 ± 10.67 years COPD diagnosed by GOLD criteria were evaluated for frequency of anaemia. In addition to baseline investigations. Erythropoietin and Hepcidin levels, CRP level Iron profile and serum ferritin level also measured of studied patients. To measure comorbidity associated with COPD and its association with anaemia Mmrc score and CAT score also applied to study subjects. we observed that anaemia is very common in COPD patients and further elevated serum CRP levels, decrease Hepcidin level and increase erythropoietin level can be major factors in the etiopathogenesis of anaemia in COPD patients. This has been extensively examined in our study. Correlation with CAT score and mMRC grade indicates that disease severity increases with disease progression which can affect the quality of life and can be further worsened by the presence of anaemia in COPD patients.

We observed that anemia is very common in COPD patients and elevated serum CRP levels, decreased hepcidin levels, and increased erythropoietin levels may be significant factors in the etiopathogenesis of anemia in COPD patients. This has been extensively examined in our study. The correlation with CAT score and mMRC grade indicates that disease severity worsens with disease progression, which can negatively affect the quality of life and is further exacerbated by the presence of anemia in COPD patients.

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