Review Article

Anemia in Chronic obstructive pulmonary disease: Prevalence, pathogenesis, and potential impact

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable lifestyle-related disease with high global prevalence. COPD is associated with significant morbidity and mortality worldwide. Comorbidities are important events in the natural history of the disease and have a negative effect on the morbidity and mortality of COPD patients. Cardiac diseases, lung cancer, osteoporosis, and depression are common comorbidities reported for COPD. Recently, anemia has been recognized as a frequent comorbidity in COPD patients. The prevalence of anemia in patients with COPD varies from 7.5% to 33%. Anemia of chronic disease (ACD) is probably the most common type of anemia associated with COPD. ACD is driven by COPD-mediated systemic inflammation. Anemia in COPD is associated with greater healthcare resource utilization, impaired quality of life, decreased survival, and a greater likelihood of hospitalization. We need large prospective studies to discern the association between anemia and COPD.

KEY WORDS: Anemia of chronic disease, anemia, chronic obstructive pulmonary disease

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INTRODUCTION

The global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (COPD)[1] defines COPD as a common preventable and treatable disease. It is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response, in the airways and the lung, to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. Systemic effects and/or comorbidities are important events in the natural history of the disease and have a capacity to increase the morbidity, economic burden, and mortality of COPD. Comorbidity is a disease process coexisting with COPD and is probably due to common risk factors. When coexisting illnesses are a direct consequence of the patient's underlying COPD, it is called a systemic effect.[1,2] Therefore, the systemic effects of COPD are direct consequences of the disease with a cause-and-effect relationship. Screening of the comorbidities should be an important component in the management of a COPD patient.

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The factors that have been linked to systemic consequence and comorbidities in COPD patients are systemic inflammation and shared risk factors, smoking and physical inactivity/deconditioning.[2] Systemic inflammation is a widely studied topic in COPD and has been potentially linked to comorbidities. Systemic inflammation in COPD may be the direct consequence of a systemic 'spill-over' of the ongoing pulmonary inflammation. Second, COPD is a part of the chronic systemic inflammatory syndrome[3] and pulmonary manifestations are one part of the multiple organ compromise, due to the consequences of systemic inflammation. Systemic manifestations and comorbidities commonly reported in COPD include cardiovascular disease, malnutrition, osteoporosis, gastroesophageal reflux, and clinical depression and anxiety.[4] In recent years, anemia has become another comorbidity that has gained importance in patients with COPD. Traditional teaching in clinical medicine considers polycythemia to be a common adverse event of hypoxemia in COPD.

However, nowadays this occurs less frequently due to more rigorous correction of hypoxemia by domiciliary long-term oxygen therapy.[5] Conversely, anemia has been reported more frequently in association with COPD in recent years with an impact on the quality of life (QOL), healthcare utilization, and survival.[6] This review will focus on various causes of anemia, its pathogenesis, and its impact on patients with COPD.

The World Health Organization's (WHO) definition of anemia is based on a hemoglobin level of less than 13 g/dL in men and 12 g/dL in women.[7] No study has been reported for any specific cut off in the setting of COPD and hypoxemia, as we know that hypoxemia can increase the hemoglobin level. Anemia is known to occur in many chronic conditions such as chronic heart failure, rheumatoid arthritis, cancer, chronic infections, chronic kidney disease, and many other chronic inflammatory conditions. However, anemia has gained importance in COPD over the last one decade only. Anemia in COPD can have various causes. Anemia of chronic disease (ACD) is probably the predominant mechanism of anemia related to chronic systemic inflammation of COPD. Prevalence of anemia in the general population increases with age and COPD is a disease that affects the aging population. Therefore, anemia in COPD may also be related to the aging process. Finally, in developing countries, anemia has a higher prevalence. There may be some overlapping effect in terms of its prevalence in COPD.

PREVALENCE OF ANEMIA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Prevalence of anemia in COPD has been reported to vary from 7.5 to 33% as shown in Table 1. Most of the studies reported in Table 1 are retrospective in nature. John *et al*.[8] observed anemia in 13% of 101 COPD patients and they pathogenetically related it to the presence of inflammation. Anemia was normocytic and normochromic in nature. Halpern *et al*.,[9] by using the US Medicare claims database, reported anemia in 21% of 132,424 patients with a COPD diagnosis. The most recent hospital-based cross-sectional study by Parveen *et al*.[10] reported anemia in 18% of the patients. Shorr *et al*. in a retrospective data analysis of 2404 COPD patients from USA reported a very high frequency of anemia, of 33%.[11] Therefore, anemia is definitely a common entity in COPD patients, unlike the traditional view of polycythemia, that is given more emphasis in almost all standard textbooks. The frequency of anemia in COPD patients is variable in literature, reflecting various methods of studies, outpatient versus hospitalized patients, stable versus patients in acute exacerbation of COPD, local prevalence of anemia, the confounding factors, and different definitions of anemia adopted in these studies. There is, therefore, a need to perform a standardized study to find out the frequency of anemia in COPD. John *et al*. also compared the prevalence of anemia in hospitalized patients with various chronic diseases. Unlike COPD, anemia has been a widely studied subject in heart failure, rheumatoid arthritis, and cancer. The overall prevalence in COPD patients was 23.1%, whereas, prevalence in patients with chronic heart failure was 23.3%. Patients with renal insufficiency and cancer presented the highest frequencies of anemia, of 71.8 and 45% respectively.[12]

PATHOGENESIS OF ANEMIA

Erythropoiesis in COPD can be affected by various factors and it can manifest by either anemia or polycythemia.[18] Development of anemia or polycythemia depends on the balance between inflammatory stimuli and hypoxic stimuli. Anemia is more common than polycythemia, and the Association Nationale pour le Traitement a Domicile del'Insuffisance Respiratoire Chronique (ANTADIR) study[13] revealed anemia and polycythemia in respectively 13.6 and 8.4% of the patients with COPD (hematocrit less than 39% and more than 55%, defining anemia and polycythemia, respectively). The World Health Organization defines anemia in the general population as a hemoglobin concentration of less than 13.0 g/dL in men and less than12.0 g/dL in women.[7] The following issues must be kept in mind while studying anemia in COPD. COPD is a chronic disease with increasing prevalence in the aging population. Prevalence of anemia also increases with age in the general population. The National Health and Nutrition Examination Survey (NHANES-III) observed a prevalence of anemia of 11% and 10.2% in men and women, aged 65 years and older, respectively.[19] Iron-deficiency anemia in particular, is a major problem in developing countries.[20] Therefore, it will not be surprising to see some overlapping effect. There is also controversy regarding the appropriate hemoglobin threshold for anemia in post-menopausal females. Finally, hypoxemia in COPD may be responsible for the phenomenon of 'relative anemia,' by apparently elevating the hemoglobin values.[21] Hypoxia via the hypoxia inducible factor (HIF) increases erythropoietin (EPO) production in the proximal convoluted cell of the kidney. The EPO decreases apoptosis of the red blood cell (RBC) stem cells and increases their survival.[22] Hypoxia at the same time inhibits hepcidin secretion to increase iron delivery to the bone marrow. Hepcidin normally inhibits iron release from the hepatocyte.[23] The role of hepcidin will be discussed in detail later. The exact cut-off of anemia in the setting of hypoxemia and inflammation in COPD patients is not known.

Mechanisms of anemia in COPD are probably multifactorial. They may be anemia of chronic disease related to inflammation, iron and vitamin deficiency, comorbidities, hypogonadism or treatment related.[18]

Most of the literature has placed emphasis on anemia of chronic disease or anemia of inflammation as the predominant mechanism for development of anemia in COPD. Anemia of chronic disease (ACD) is an

Table 1: The frequency of anemia in various studies

Author/ Country and year of study	Design of study	Definition of anemia	COPD diagnosis	Exclusion criteria	Total patients of COPD and no(%) of anemics
John *et al.*[8] Germany, 2005	Prospective outpatient	Hemoglobin levels: Male <13.5 mg/dl Female <12.0 mg/dl	Spirometry-based	Current or past diagnosis of asthma and a respiratory tract infection in the previous three months Patients with cancer, thyroid disease, severe liver disease, and chronic heart failure Patients with a history of GI hemorrhage or blood loss of any other cause Patients with a known vitamin B12 or folic acid deficiency	Total patients: 101 Anemic: 13 (12.9%) patients
Halpern *et al.*[9] USA, 2006	Retrospective US Medicare claims database	ICD-9 codes specific for anemia, or receipt of blood transfusions not associated with other apparent causes (e.g., acute blood loss from surgery, trauma, etc.)	Diagnosed by physician/ supplier or outpatient file	Under age 65 Not a United States resident Known nutritional or hereditary anemia Disease associated with anemia	−132,424 21% (27,932) had anemia
Parveen[10] Kashmir, India, 2010	University hospital-based cross-sectional study	Hb level: <13.5 gm/dl in male patients <12 gm/dl in female patients	Clinical and spirtometric criteria	All patients with insufficient mental capacity that precluded obtaining an informed consent from them current or past diagnosis of asthma Patients with cancer, thyroid disease, severe liver disease, chronic kidney disease, chronic heart failure, rheumatoid arthritis, GI hemorrhage or blood loss of any other cause Patients with a known vitamin B12 or folic acid deficiency	−200 COPD patients 36 cases (18%) of anemia
Shorr *et al.*[11] USA, 2008	Retrospective cohort study	Hb <12 g/dL for females Hb <13 g/dL for males	ICD-9	Receiving cancer therapy Hemoglobinopathies Nutritional deficiencies	−2404 patients with COPD −788 (33%) had anemia
Chambellan[13] France, 2005	Retrospective	Hematocrit: <39% in men; < 36% in women	Clinical and spirometry-based	Not specified	−2,524 COPD patients −264 men (12.6%) had hematocrit <39%
Krishnan *et al.*[14] New York, 2006	Retrospective	Hb level Men: <13 mg/dl Women: <12 g/dl	Spirometry-based	Missing pulmonary function tests Missing hemoglobin results Missing health-related quality of life score Pulmonary function tests results not acceptable or reproducible Race other than white or black Missing information on height, smoking status, pack-years, or education	COPD 495 patients 37 had anemia (7.5%)
Cote *et al.*[15] USA , 2007	Hb data were collected retrospectively, while all other data were collected Prospectively from the BODE study cohort	Hb levels: <13 g/dL for males and females	History of smoking >20 pack-years Ratio of FEV1 to FVC <0.7	Illness other than COPD likely to cause death within three years: Asthma MI in the past three months Unstable angina/congestive heart failure	−677 patients, 116 (17.1%) were anemic
Attaran[16] Iran, 2009	Observational study	Hb level: Male <13.5 mg/dl Female <12.0 mg/dL	Spirometry-based	Asthma, cancer, severe liver or kidney diseases, left heart failure or other chronic diseases History of gastrointestinal bleeding or blood loss of any other cause B12 or folic acid deficiency, low serum ferritin levels	−13 of 80 patients had anemia (16%)
Boutou[6] Greece, 2012	Case-control design	Hb levels: Males: <13 mg/dl Females: <12 mg/dl	Clinical and spirometry-based	Acute or chronic infection systemic inflammatory or autoimmune disorders other than COPD Kidney disease Thyroid disease Liver cirrhosis	−44 patients and 27 had ACD
Silverman[17] Israel, 2014	Retrospective data analysis	Hb <12 g/dl	Diagnosed COPD patients	Not specified	Of 107 consecutive patients hospitalized with an AECOPD,47 (43.9%) were anemic

COPD: Chronic obstructive pulmonary disease, ICD: International classification of disease, GI: gastrointestinal, ACD: Anemia of chronic disease, FVC: Forced vital capacity, BODE: Body mass index, airflow obstruction, dyspnea and exercise capacity

immune-mediated phenomenon that occurs in many chronic disease processes; for example, infection, autoimmune diseases, cancer, chronic kidney disease, and so on.[24] Inflammation being an important pathogenetic mechanism, ACD is often regarded as 'anemia of inflammation' and is present in many chronic inflammatory conditions. ACD is usually a mild-to-moderate, normochromic, normocytic anemia, characterized by low iron and normal-to-low transferrin levels, with adequate reticuloendothelial iron stores (normal or increased ferritin level).[25] The possible mechanisms that have been incriminated in causing ACD are: Iron homeostasis dysregulation, blunted endogenous erythropoietin production, impaired bone marrow erythropoietic response, and shortened RBC survival.[24]

IRON HOMEOSTASIS DYSREGULATION

An important diagnostic feature of ACD is hypoferremia or low serum iron levels in the setting of adequate or increased iron stores in the reticuloendothelial system (RES).[26] It occurs due to the increased uptake and retention of iron within the RES, coupled with impaired iron mobilization, ultimately culminating in reduced availability of iron for the erythroid progenitor cells in the bone marrow and development of iron-restricted erythropoiesis.[27] The main factor involved in this pathophysiological mechanism of ACD is hepcidin. Hepcidin is a type-II 25 amino acid disulfide-rich peptide, that is produced in the liver, and is an acute-phase protein.[28,29] The liver is the main source of hepcidin production, but macrophages and adipocytes also secrete small amounts of Hepcidin.[30,31] Hepcidin is the key regulator of iron metabolism. It regulates the plasma iron level by various mechanisms. It inhibits intestinal iron absorption and placental iron transport.[32] It also inhibits the release of recycled iron from macrophages[33] and the hepatic storage site.[34] Ultimately, it inhibits delivery of iron to the maturing erythrocytes in the bone marrow. All these mechanisms may lead to iron-restrictive anemia seen in chronic inflammation. It is important to know how iron is released from various cells in the body to understand the mechanism of action of hepcidin. Iron is released from the duodenal enterocyte, macrophage, and hepatocyte via a special membrane iron exporter called ferroportin. Hepcidin modulates the ferroportin level posttranslationally by binding to the ferroportin and induces its internalization and degradation in lysosomes as shown in Figure 1.[35] This Hepcidin–ferroportin interaction is responsible for trapping iron in the hepatocytes, macrophages, and absorptive enterocytes in the duodenum. There are various regulators for hepcidin synthesis. Plasma iron overload, Interleukin 1(IL-1) and IL-6, and Lipopolysaccharides (LPS) stimulate hepcidin synthesis, while it is inhibited by tumor necrosis factor (TNF)-α, anemia, and hypoxia.[36-38]Interleukin-6 is a pleiotropic cytokine that affects immune response, inflammation, and hematopoiesis.[39] Among all the cytokines, IL-6 is a major contributor of hepcidin synthesis via the STAT3 (signal transducers and activators of transcription protein 3) signal.[40] Animal studies in IL-6 knockout mice have further proved the role of IL-6 in hepcidin production. It has been seen that IL-6 knockout mice fail to produce hepcidin in response to inflammatory challenges, unlike that which normally occurs in wild-type mice.[36] Regarding the role of IL-1, there is a controversy. Nemeth *et al*. observed that IL-1 had no stimulatory effect on hepcidin expression in the human hepatocyte, but Inamura *et al*. reported that IL-1 played a significant role in hepcidin synthesis.[41]

STUDIES OF INTERLEUKIN-6/HEPCIDIN AXIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

John *et al*.[8] measured the inflammatory parameters in anemic and non-anemic COPD patients and the controls. They observed a significantly higher level of inflammatory parameters in anemic COPD patients compared to the control subjects, IL-6 ($P < 0.0001$) and C-reactive protein (CRP) ($P < 0.001$). Comparing anemic and non-anemic COPD patients, they found a significantly higher CRP level in the anemic group ($P < 0.001$), whereas, IL-6 did not differ between both groups, although the level was higher in anemic COPD patients. Similarly, Boutou *et al*.,[6] in a case control study, observed significantly higher levels of IL-10 and Interferon gamma (IFN-γ). The levels of IL-1b and IL-6 were also higher in COPD patients with anemia of chronic disease, but the differences did not reach a statistical significance. There could be various reasons for the non-significant rise in the IL-6 level in various studies. In normal healthy subjects, the serum IL-6 concentrations are quite low (0.2–7.8 pg/ml). Immunoassay for IL-6 lacks sensitivity.[42] Monoclonal antibodies used in the assay might differ in their recognition of the different IL-6 isoforms, monomer or multimers. They are also sensitive to interference by various plasma components, for example, the soluble IL-6 receptor (sIL-6R).[43] Thompson *et al*. evaluated four IL-6 assays and showed that not all the assays performed equally well, with the newer types

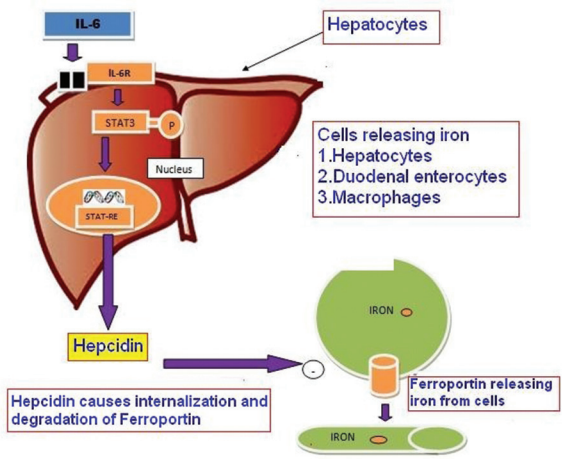

Figure 1: The IL-6/Hepcidin/Ferroportin axis

of technologies performing better.[44] Another reason for the discordance between the IL-6 and hepcidin levels may be the presence of other regulators of hepcidin synthesis. In multiple myeloma, BMP2 has been shown to be the major regulator,[45] and Activin B has been shown to be an important regulator in the mouse model of inflammation.[46] However, it definitely requires further study of COPD patients to prove the role of BMP2 and Activin B as alternate hepcidin regulators.

Few studies measured the hepcidin level in COPD patients. Duru *et al*.[47] reported a decreased hepcidin level with increased severity of COPD compared to mild COPD and healthy controls. The decreased hepcidin level could be an attempt to lessen the impact of hypoxemia in severe COPD. On the other hand, Mumby *et al*.[48] noted a higher serum hepcidin level in COPD patients compared to the healthy controls. The discrepancy between the two studies may be explained by the methods of the hepcidin assay used. Duru *et al*. measured the pro-hepcidin assay (prohormone enzyme immunoassay kit RE 54051, IBL). The pro-hepcidin levels did not correlate with the urinary and serum mature bioactive 25-amino acids hepcidin levels, nor did they respond to the relevant physiological stimuli.[49-52] Pro-hepcidin was also not stable in the plasma.[53] Moreover, pro-hepcidin was unable to degrade the iron exporter ferroportin unless maturated by a furin-dependent process.[54] Mumby *et al*. used the enzyme-linked immunosorbent assay (ELISA) method to measure the serum hepcidin level.

There are various hepcidin assays in the market. The first International Round Robin exercise for comparing the measurements of hepcidin among different assays worldwide has highlighted the problem of variability among various assays.[55] Therefore, we need highly validated standardized methods of measurement of various cytokines and acute phase products for better delineating their role in the development of anemia in COPD.

IMPAIRED BONE MARROW RESPONSE TO ERYTHROPOIETIN

In ACD, the proliferation and differentiation of erythroid precursors in the bone marrow are impaired. This may be due to reduced or impaired erythropoietin (EPO) production and the effect of inflammatory cytokine-mediated diminished erythropoietin (EPO) on the bone marrow. Cytokines such as IL-1 and TNF-α inhibit the renal EPO production by cytokine-mediated formation of the reactive oxygen species (ROS), which has a negative impact on the binding affinities of the transcription factors for EPO production and also damages the EPO-producing cells.[56]

Moreover, IL-1, TNF-α, and INF-γ blunt the erythroid progenitor response to EPO. INF-γ causes apoptosis of the erythroid progenitors and also downregulates the EPO receptor expression.[57] John *et al*.[8] have observed an inverse correlation between hemoglobin and the EPO levels, reflecting the presence of resistance to the action of EPO. Erythropoietin is significantly elevated in the anemic group compared to the non-anemic patients (41.8 ± 25.4U/L vs. 16.3 ± 2.9U/L) and normal subjects (41.8 ± 25.4U/L vs. 11.3 ± 1.6U/L) [$P < 0.05$]. Boutou *et al*. have similarly observed significantly higher erythropoietin levels in patients with ACD than in the controls, indicating erythropoietin resistance.[58] A blunted response to erythropoietin in COPD is also increased with the advancement of COPD.[59] The blunted EPO response in COPD is a temporary phenomena, as once the inflammation subsides, the response to EPO is restored. Markoulaki *et al*.[60] have measured the levels of hemoglobin, EPO, and biomarkers of systemic inflammation in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (AECOPD), during resolution and in stable condition. There is a negative association in the acute condition between the Hb level and EPO level, clearly indicating the development of EPO resistance. This inverse relation between the Hb and EPO levels during the acute stage becomes a positive association during discharge and the stable phase.

SHORTENED RED BLOOD CELL SURVIVAL

Shortened RBC survival is mediated by inflammatory cytokines, such as interleukin-1 (IL-1), produced by activated macrophages. It augments the ability of macrophages to ingest and destroy red cells, particularly through a selective hemolysis of newly formed erythrocytes, called neocytolysis.[61,62] In animal models and *in vitro* studies, TNF has also been implicated in reducing RBC survival.[63]

OTHER FACTORS CAUSING ANEMIA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

Renal dysfunction

Chronic renal failure (CRF) is a known cause of anemia as shown in Figure 2. Studies have shown the presence of chronic renal failure as a comorbidity in COPD patients

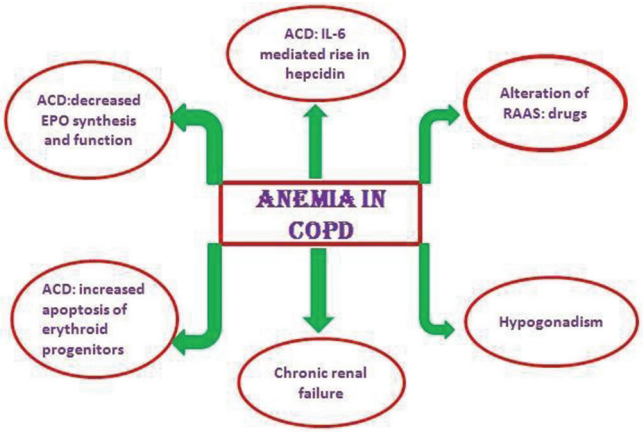

Figure 2: Various mechanisms of anemia in COPD

and may explain the coexistence of anemia in COPD.[64,65] Incalzi *et al*.[64] reported a prevalence of concealed and overt CRF in elderly patients with COPD, aged 65 years and older, by 20.8 and 22.2%, respectively. CRF can cause anemia by impairment in the production of erythropoietin by proximal convoluted cells.[66]

Drugs and the renin-angiotensin-aldosterone system

Various drugs may cause anemia via an effect on the renin-angiotensin-aldosterone system (RAAS). The renin-angiotensin-aldosterone system is an important factor affecting hematopoiesis. RAAS regulates erythropoiesis via two mechanisms: Angiotensin II acts as a growth factor for erythroid progenitors in the bone marrow. Second, Angiotensin II stimulates erythropoietin secretion.[67] Activation of RAAS may explain the development of secondary erythrocytosis in patients with COPD and chronic hypoxemia.[67] Alteration in the activation of RAAS via ACE inhibitors and AT1 receptor blockers may explain anemia in COPD patients.[68,69] Theophylline also has the potential to affect erythrocytosis in patients with COPD. One mechanism is modulation of EPO production via adenosine receptor A_2 antagonism.[70] Tsantes *et al*., however, did not find support for this hypothesis. They reported significantly lower hemoglobin levels in COPD patients treated with theophylline than those not on theophylline ($P < 0.05$). Serum EPO levels did not differ between the studied groups. They proposed a direct inhibitory action of theophylline on erythropoiesis, possibly via enhanced apoptosis.[71]

Effect of hypogonadism

Prevalence of hypogonadism in men with COPD varies from 22 to 69%.[72-75] Ferrucci *et al*. noticed that older men and women with low testosterone levels had a higher risk of anemia.[76] There are various mechanisms by which low testosterone causes anemia. First, testosterone stimulates erythropoiesis by enhancing the proliferation of erythroid progenitors via a specific nuclear steroid responsive element, in a dose-dependent manner. Testosterone may also exert EPO stimulatory activity.[76] Testosterone can also augment erythropoiesis via the stimulation of RAAS.[77]

Anemia in COPD has negative impact on various clinical parameters.

IMPACT ON QUALITY OF LIFE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

Health-related quality of life (HRQOL) consists of physical, psychological, and social domains of health across stages.[78] It has become an important tool in the assessment of COPD patients.[79] Krishnan *et al*.[14] retrospectively analyzed the relationship between anemia in COPD and HRQL among patients enrolled from the general population in New York city. This study used a generic instrument, SF-36, rather than a disease-specific QOL instrument. The prevalence of anemia was lower compared to other studies, 8% among 495 patients with moderate-to-severe COPD. However, COPD patients with anemia showed significantly lower physical functioning scores ($P = 0.002$) and physical component summary scores ($P = 0.02$).

The limitation of this study is that some of the disease processes that may confound the results are not adjusted, for example, congestive heart failure and neuromuscular disorders. Fatigue is an important symptom in COPD, present in 43 to 58% of the patients with COPD.[80]Anemia is also associated with fatigue and dyspnea; both symptoms have a negative impact on the QOL of COPD patients. Cote *et al*.[15] also reported anemia in COPD as an independent risk factor for reduced functional capacity.

IMPACT ON HOSPITALIZATION, COSTS, FUNCTIONAL STATUS, AND MORTALITY

Anemia in patients with COPD is also a risk factor for readmission to hospital. Barba *et al*.,[81] in a retrospective data analysis from the Spanish cohort of COPD patients, reported a 25% higher risk of readmission in them, than in non-anemic COPD patients. It is also important to note that the impact of anemia is independent of the effect of the confounders, for example, age of the patient, gender, and other comorbidities. Therefore, anemia is also an important factor in the natural history of COPD, due to the increased risk of hospitalization and subsequent escalating cost and other effects of hospitalization. Greater use of healthcare resources and increased cost of care has also been mentioned by Halpern *et al*.[9] This is also a retrospective data analysis based on US Medicare claims database (1997 – 2001). They also noted higher comorbidities and older age among anemic COPD patients. The mortality rate among anemic patients is also two-fold higher than non-anemic COPD patients. The limitation of this study includes lack of availability of data of pulmonary function testing for these patients; therefore, the impact of anemia could not be assessed independent of the severity of airflow obstruction. Martinez-Rivera *et al*.[82] studied the impact of anemia on patients admitted with acute exacerbation of COPD (AECOPD) and followed them for one year. They noticed a very high prevalence of anemia of 33% in AECOPD patients. Anemia and previous exacerbations were reported as independent predictors of mortality. It is important to know the variables associated with poor prognosis in AECOPD patients as it will help in taking necessary interventions to ameliorate the detrimental effect of AECOPD on human health. Cote *et al*.,[14] in a retrospective analysis of data from the Burden of Disease Epidemiology (BODE) study cohort reported a significantly higher modified Medical Research Council dyspnea scale score (2.8 vs. 2.6), lower six-minute walk distance (265 vs. 325 m), and shorter median survival (49 vs. 74 months) in anemic patients than non-anemic patients. Anemia in COPD patients is an independent risk factor for reduced functional capacity. However, the problem with data

analysis with most of these studies is their retrospective design, so inherently subjected to many biases. Anemia was not identified as an independent predictor of survival in this cohort.

Boutou *et al*.,[83] in a retrospective study of stable COPD patients, reported the presence of anemia as being significantly associated with survival, independent of age and FEV_1 percentage of predicted. The median survival rates in anemic and non-anemic COPD patients were 68.7 (18.1 – 91.5) months and 79.8 (57.5 – 98.4) months, respectively, $P = 0.035$. Surprisingly, the hemoglobin (Hb) concentration, when treated as continuous variables, was neither univariately nor multivariately associated with mortality. The authors proposed that in a scoring system, anemia should be used as a categorical rather than a continuous variable.

Anemia is also a risk factor for increased mortality among COPD patients admitted in the Intensive Care Unit (ICU) and requiring invasive mechanical ventilation. Anemia is defined by a single cutoff of < 12.0 g/dL for both men and women. The overall 90-day mortality among anemic COPD patients was 57.1% versus 25% in non-anemic patients, and the adjusted 90-day mortality rate ratio (MRR) was 2.6.[84] Chambellan *et al*.[13] studied the association between the hematocrit and prognosis in 2524 patients with severe COPD, receiving long-term oxygen therapy. The database is derived from the French respiratory homecare network, ANTADIR. They reported anemia in 12.6% of males and 8.2% of females among 2,524 COPD patients, with a $PaO_2 < 55$ mmHg. These patients developed anemia despite having persistent hypoxemia, clearly indicating an inflammatory response stronger than the hypoxemic stimulation of erythropoietin secretion. Hematocrit decreased with increasing age and severity of airway obstruction. Multivariate analysis demonstrated that decreased hematocrit was an independent predictor of survival. The anemic COPD patients were associated with decreased long-term survival, increased frequency of hospitalization and longer mean hospital stay than non-anemic COPD patients. The relative risk of death was lessened by 14% with every 5% increase in hematocrit. The limitation of this study had two factors. Only severe COPD was included and comorbidities were not included as covariates. It was once again retrospective in nature. The finding from the ANTADIR study that survival in polycythemic COPD patients was better than in anemic patients with COPD was also echoed by the Kollert *et al*. study.[85]

Anemia also depicted a poor prognosis in COPD patients undergoing surgery or in those who had developed some acute event. Upchurch *et al*.[86] studied the risk factors associated with an unfavorable outcome after elective abdominal aortic aneurysm (AAA) repair in patients with COPD. The following factors were identified to be associated with unfavorable outcomes after open elective surgical repair of AAA, for example, fewer prescribed inhalers, lower hematocrit, renal insufficiency, and coronary artery disease. Therefore, correction of anemia should be an important preoperative goal in order to avoid an unfavorable postoperative outcome in COPD patients. Cappell *et al*.[87] in a case–control study reported significantly higher mortality in COPD patients as compared to controls with gastrointestinal bleeding (mortality in COPD 32%, controls 10%). The study on COPD patients showed that they had a significantly higher likelihood of being older, smokers, alcoholics, and taking corticosteroids, than the controls. However, increased mortality was still present, even after adjusting these confounders. The increased mortality may be due to the fact that COPD patients, who already have preexisting tissue hypoxia, may be more sensitive to the detrimental effects of anemia. It may also be due to greater blood loss during surgery. Anemia, therefore, is an important factor in patients with COPD, in terms of increased morbidity, mortality, escalating healthcare costs, and poor outcome after a major surgical procedure. Correction of anemia definitely should be an important goal in the management of COPD. The impact of anemia in patients of COPD is shown in table 2.

IMPACT OF CORRECTIONS OF ANEMIA

Schönhofer *et al*.[88] studied the impact of blood transfusion on minute ventilation (V'E) and work of breathing (WOB) in 20 anemic adults (hemoglobin of <11 g/dl). Ten patients had severe COPD and ten patients had no underlying lung disease. In patients with COPD, blood transfusion caused a reduction in the mean V'E from 9.9 ± 1.0 to 8.2 ± 1.2 L/minute (P <.0001), and WOB was reduced from 1.03 ± 0.24 to 0.85 ± 0.21 WOB/L (P <.0001). In anemic patients without lung disease, minute ventilation and WOB did not change after the increase in hemoglobin, to a similar degree. Therefore, in COPD patients with anemia, blood transfusion leads to a significant reduction of both V'E and WOB. One interesting finding is the development of hypercapnia after transfusion. A low hemoglobin level stimulates alveolar ventilation and may thus be responsible for the low $Paco_2$ level. Transfusion by increasing the hemoglobin level may suppress ventilation and cause hypercapnia. Blood transfusion may also lead to successful weaning in ventilated COPD patients with anemia.[89] Schönhofer *et al*.,[89] in 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. Therefore, correction of anemia should be an important goal in the management of COPD.

Table 2: Impact of anemia in COPD patients

Greater use of healthcare and increased cost of care[9]
Longer mean hospital stay[13]
Poor health related quality of life (HRQOL) and functional status[14,15]
Increased risk of hospitalization
Poor survival[15,83]
Worse prognosis in patients undergoing surgery or battling an acute event.[86,87]

COPD: Chronic obstructive pulmonary disease

MECHANISMS OF IMPROVEMENT AFTER CORRECTIONS OF ANEMIA

- Reduction in minute ventilation (V'E) by blood transfusion may lead to a decrease in dynamic hyperventilation in COPD and subsequent improvement in dyspnea and exercise tolerance[90]
- Increase in the hemoglobin level may lead to better oxygen delivery to the tissues, resulting in a better skeletal muscle function and subsequent improvement in the exercise capacity. Correction of the hemoglobin level can also lead to improvement in gas exchange at the alveolocapillary membrane.

OTHERS ALTERATION IN RED BLOOD CELLS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Red blood cell macrocytosis, defined as the mean corpuscular volume (MCV) higher than 94 fl, has been reported in patients with COPD. The exact mechanism of high MCV is not clear, although it has been reported as early as 1972, by O'Neil *et al*.[91] Tsantes *et al*.[92] have studied this issue in detail in 32 clinically stable patients with hypoxemic COPD and 34 healthy volunteers. Macrocytosis (defined as MCV > 94 fL) was found in 43.75% of the patients with COPD and 37% of this group had erythrocytosis. The authors proposed that recurrent erythropoietic stress that occurs in COPD as a result of exacerbations and nocturnal or exercise-related desaturation, acts as a trigger for the release of immature cell forms of RBCs, to optimize the oxygen-carrying capacity. Pachón *et al*.[93] have reported a prevalence of macrocytosis of 29%. No correlation has been found between MCV and arterial oxygen saturation. The most interesting finding, however, is the significant correlation between macrocytosis, dyspnea, and forced expiratory volume in 1 (FEV_1) in a subgroup of nine ex-smokers (36%), a finding that suggests a correlation between macrocytosis and deterioration in the clinical situation. Another alteration of red blood cells in COPD is the variability in the size of the circulating red blood cells measured by red cell distribution width (RDW). The RDW is elevated in conditions of ineffective red cell production, increased red cell destruction, and after a blood transfusion. Patients of COPD develop RDW, due to inflammation and oxidative stress. Seyhan *et al*.[94] reported that elevated RDW levels are associated with increased mortality risk in patients with stable COPD. Alexandre *et al*.[95] have analyzed the erythrocyte membrane proteome and noticed several abnormalities in the RBC membrane in COPD patients. Methemoglobin reductase has also been found to be unexpressed in these cells, suggesting that COPD patients may be at higher risk for developing methemoglobinemia.

CONCLUSION

Anemia is a common comorbidity in patients with COPD, with prevalence varying from 7.5 to 33%. Anemia has been found to have an impact on the quality of life, healthcare resource utilization, costs, and mortality. The mechanism of anemia in COPD is probably anemia of chronic disease involving the hepcidin–ferroportin axis and cytokine-mediated development of erythropoietin resistance. Difficulty in interpretation of most of the studies is their retrospective nature, thereby, subjected to various forms of biases. We definitely need a large prospective study to determine the actual prevalence of anemia in COPD, consequences of anemia in COPD patients, and impact of correction of anemia in the clinical outcomes.

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