

Impact of Anemia on Dyspnea Severity, Systemic Inflammation, and Exercise Capacity in Chronic Lung Disease: A Cross-Sectional Observational Study

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Received: 14 Mar 2026/ Revised: 24 May 2026/ Accepted: 19 Jun 2026

ABSTRACT

Background: Chronic lung diseases (CLD) include chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and bronchiectasis and have been observed to be commonly accompanied by anaemia, which can contribute to worsening of breathlessness, inflammation, and physical exercise intolerance. This study was conducted to assess the influence of anaemia on breathlessness severity, inflammation, and functional exercise intolerance in chronic lung disease.

Methods: The study was cross-sectional observational study performed among 90 patients suffering from COPD, ILD, or bronchiectasis in a tertiary care hospital. The levels of haemoglobin, CRP, ESR, mMRC dyspnoea score, and 6MWT distance were measured. Independent t-test, chi-square test, and Spearman's correlation were used for analysis of data with statistical significance defined at $p < 0.05$.

Results: Total 90 patients, the mean age was 60.8 ± 9.2 years with COPD constituted 53.3% of the diagnoses. Anaemia was found to be prevalent in 55.6% of the subjects and was correlated with significantly lower levels of haemoglobin, higher mMRC dyspnoea score, higher CRP and ESR values, and shorter distance walked during 6MWT compared to non-anaemic subjects ($p < 0.001$ for all comparisons).

Conclusion: The study concluded that the anaemia was associated with high dyspnea, systemic inflammation and reduces the capacity of exercise among chronic lung disease patients.

Key-words: Anaemia, Chronic lung disease, Dyspnoea, Inflammation, Six-minute walk test (6MWT)

INTRODUCTION

The chronic lung diseases (CLDs), such as chronic obstructive pulmonary diseases (COPDs) and interstitial lung diseases (ILDs), constitute a significant public health problem in India due to the severe complications associated with dyspnea and poor functioning [1,2]. In Indian cohorts with gained ILD, reduced diffusing capacity is a strong predictor of poorer walking distance

and health-related quality of life, making exercise intolerance an important factor in a patient's experience [1]. The country contributes to as much as 32% of the overall chronic respiratory disease burden in terms of the years lived with disability (DALY) [2]. This considerable amount implies the need for understanding comorbidities like anemia, which are known to aggravate hypoxia leading to higher levels of breathlessness and disability [2].

Reduced hemoglobin (Hb) mass reduces arterial oxygen content (CaO₂) resulting in patient hypoxia even in normal resting saturation conditions [3]. To maintain systemic delivery, this (CaO₂ deficit activates chemoreceptors causing hyperventilation which leads to increased minute ventilation (VE) pressure which leads

How to cite this article

Parashuram, Faseeh KM, Sankar K. Impact of Anemia on Dyspnea Severity, Systemic Inflammation, and Exercise Capacity in Chronic Lung Disease: A Cross-Sectional Observational Study. SSR Inst Int J Life Sci., 2026; 12(4): 10394-10400.



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to loss of efficiency while breathing and exacerbates dyspnea ^[4,5]. During submaximal outdoor exercise such as 6-Minute Walk Test (6MWT), the lack of oxygen to the tissues makes the transition to anaerobic glycolysis faster which helps create lactate faster and affects the oxidative phosphorylation of the skeletal muscle ^[5,6].

This process limits the amount of work that the muscles can perform and leads to big desaturation during the exercise which creates significant problems for patients ^[6]. In other words, anemia causes different kinds of compensation which allow maintaining normal resting delivery but nevertheless leads to failure of normal functioning in patients engaged in physical activity ^[4]. Systemic inflammation is an integral link in the mechanism that connects chronic lung disease (CLD) to anemia of chronic disease ^[7,8].

Finally, the process disrupts hematological balance, making CLD-induced anemia essentially inflammation-driven with the circulatory cytokines interfering in iron utilization and supporting the development of anemia, adding to systemic disease burden overall ^[7, 8]. The presence of chronic pulmonary inflammation increases interleukin-6 levels which in turn trigger the liver to produce hepcidin that binds iron in macrophages and reduces absorption of iron from the intestines ^[9]. This pathway ultimately leads to the iron deficiency functional anemia and suppresses erythropoiesis that results in the anemia of chronic disease despite the availability of normal iron level in the body ^[9].

As a result, systemic inflammation acts as a double-edged sword in lung disease in that it leads to development of the damage conducted by cytokines and aggravates the symptoms of anemia and sarcopenia due to the effect of hepcidin on iron absorption from the gut and have impact on iron metabolism ^[9, 10]. The long-lasting signals that lead to inflammation also cause reduced amount of hemoglobin synthesized and slow down the processes of muscle protein exchange in the organism which results in dysfunctional exchange of oxygen in the tissues and consequently in the increase in fatigue and muscle wasting due to chronic diseases ^[9, 10]. The objective of this cross-sectional observational study is to provide a thorough assessment of the direct effect that anemia may have on the level of dyspnea, inflammatory mediators, and the level of physical activity in patients suffering from chronic lung disease.

MATERIALS AND METHODS

Research Design- The study was a cross-sectional observational study to evaluate the impact of anaemia on Dyspnea Severity patients. The study was conducted among 90 patients with more than 18 years of age. The study was conducted in a Tertiary Care Hospital for the duration of one year. Demographic, clinical, laboratory, and functional information were collected from all of the patients for the study. Those who were diagnosed and confirmed with the chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or bronchiectasis were included in the study. Well informed and written consent were taken for the study. Predefined exclusion and inclusion criteria were considered for the patient selection.

Inclusion criteria

- ✓ Patients of age above 18 years of age were included in the study.
- ✓ Those who were diagnosed and confirmed with the chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or bronchiectasis were included in the study.
- ✓ Informed consent was taken for the study.

Exclusion criteria

- ✓ Patients with the acute exacerbation of chronic lung disease within the previous 4 weeks were excluded.
- ✓ Patients with the past history of blood transfusion or known haematological disorders which had affected their haemoglobin levels were excluded.
- ✓ Those who were diagnosed with the renal diseases were excluded.
- ✓ Incomplete clinical data were not considered for the study.

Procedure- Informed consent was taken from all study participants. All of the patients were conducted with the clinical and laboratory assessment. The Haemoglobin levels was measured by the use of the automated haematology analyser and anaemia was termed as the haemoglobin <13 g/dL in males and <12 g/dL in females. C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were utilized for the evaluation of the systemic inflammation. The Medical Research Council (mMRC) dyspnea scale was used to evaluate the severity of dyspnea.

The standardized Six-Minute Walk Test (6MWT) was used to assess the functional exercise capacity. All demographic, clinical, laboratory, and functional information were collected and analyzed to identify the association of anaemia with dyspnea severity, systemic inflammation and the capacity of physical exercise among chronic lung disease patients.

Statistical Analysis- The continuous variables were compared by the use of the independent samples *t*-test, while the chi-square test was used to analyse the categorical variables. Spearman's rank correlation analysis was performed to investigate the association between the variables. The *p*-value of <0.05 was considered for statistical analysis.

RESULTS

Table 1 summarized the baseline demographic and clinical parameters among 90 participants. The mean value of the age was 60.8 ± 9.2 years, whereas males were 62.2%, females were 37.8%. The most predominant diagnosis was COPD 53.3%, which was followed by the 26.7% of ILD and 20.0% of bronchiectasis. The level of haemoglobin was 12.2 ± 1.7 g/dL, while 47.8% of patients were suffering from anaemia. Participants showed the moderate dyspnea with a mean mMRC score of 2.5 ± 0.8 , which was accompanied with the high level of inflammatory markers. The mean 6-minute walk distance was 328 ± 58 m suggested the reduction in functional exercise capacity for the study population.

Table 1: Baseline Demographic and Clinical Characteristics of Patients with Chronic Respiratory Diseases (n = 90)

Variable	Value (n = 90)
Mean Age (years)	60.8 ± 9.2
Male: Female	56:34
Diagnosis – COPD / ILD / Bronchiectasis	48 / 24 / 18
Mean Haemoglobin (g/dL)	12.2 ± 1.7
Anaemia Prevalence	43 (47.8%)
Mean mMRC Score	2.5 ± 0.8
Mean CRP (mg/L)	13.6 ± 5.9
Mean ESR (mm/hr)	36.8 ± 11.4
Mean 6MWT Distance (m)	328 ± 58

Table 2 showed the comparative analysis for the clinical and functional parameters for both of the anaemic and non-anaemic patients. The first group showed low mean haemoglobin levels (10.6 ± 1.2 g/dL) compared with the non-anaemic group (13.3 ± 0.9 g/dL, $p < 0.001$). The patients in the anaemic group showed high dyspnoea, which was indicated by high mean mMRC score (3.0 ± 0.8 vs. 2.2 ± 0.7 , $p = 0.001$). High level of inflammatory

markers showed high for the anaemic patients, with high CRP and ESR values. Functional capacity was impaired in the first group, which revealed low mean 6-minute walk distance. This indicated the relationship between the anaemia, inflammation, symptom severity, and reduced exercise tolerance.

Table 2: Comparison of Clinical & Functional Parameters between Anaemic and Non-Anaemic Patients

Parameter	Anaemic	Non-Anaemic	p-value
Haemoglobin (g/dL)	10.6 ± 1.2	13.3 ± 0.9	<0.001
mMRC Score	3.0 ± 0.8	2.2 ± 0.7	0.001
CRP (mg/L)	17.2 ± 5.8	10.8 ± 4.2	<0.001
ESR (mm/hr)	42.5 ± 10.3	31.6 ± 9.7	<0.001
6MWT Distance (m)	289 ± 54	356 ± 49	<0.001

Table 3 showed the distribution of anaemia based on different mMRC dyspnea grades. 50 out of 90 patients (55.6%) were anaemic. Prevalence of anaemia showed high rate according to increased severity of dyspnoea with 25.0% of anaemia among patients in mMRC Grade 0 and 38.9% for Grade 1 and 45.8% for Grade 2. There was

an increase among patients with high dyspnea classes where the prevalence rate of anaemia was 72.7% for Grade 3 and 77.8% for Grade 4. Overall the table findings showed a positive correlation between increased severity of dyspnoea and anaemia prevalence.

Table 3: Distribution of Anaemia on the basis of the mMRC Dyspnoea Grade among 90 Patients with Chronic Respiratory Diseases

mMRC Grade	Total Patients (n=90)	Anaemic Patients (n=50)	Prevalence (%)
0	8	2	25
1	18	7	38.90
2	24	11	45.80
3	22	16	72.70
4	18	14	77.80
Total	90	50	55.60

Table 4 represented the distribution of anaemia for different chronic respiratory disease diagnoses. 53.3% of population showed the highest of COPD, which was followed by the 26.7% of ILD and 20.0% of bronchiectasis. Among 50 patients, COPD group showed highest number among 28 patients, with 58.3% of anaemia prevalence. 55.6% of Bronchiectasis, while 50.0%

showed the prevalence of ILD. Overall, 55.6% of the population was affected by anaemia. The COPD showed high burden of anaemia, with similar rate of prevalence for the diagnostic groups, which suggested that the anaemia is common comorbidity apart from the chronic respiratory disease.

Table 4: Distribution and Prevalence of Anaemia across different Chronic Respiratory Disease Diagnoses

Diagnosis	Total Patients (n = 90)	Patients with Anaemia (n = 50)	Prevalence of Anaemia (%)
COPD	48 (53.3%)	28	58.30
ILD	24 (26.7%)	12	50
Bronchiectasis	18 (20.0%)	10	55.60
Total	90 (100%)	50	55.60

DISCUSSION

In Lucknow, India, a case-control study was carried out where 150 COPD patients were included. The outcomes from the study established a prevalence rate for anemia of 31.6%, which consequently led to a decrease in hemoglobin levels among the anemic group (11.0 ± 1.1 g/dL vs 13.9 ± 0.8 g/dL) ^[11]. This drop in hemoglobin level caused a statistically significant correlation with the severity of dyspnea as evidenced by the modified Medical Research Council ^[11]. Moreover, the study also showed that patients with a lower hemoglobin level experience more acute exacerbations and hospital admissions.

Similar findings were confirmed through parallel multi-centered Indian data showing that while past cases of polycythemia have seen a decrease through time, cases of anemia continue escalating ^[12]. Different studies demonstrated that fluctuations in hemoglobin levels directly affect the level of severity of COPD cases, their respective pulmonary function status, and symptoms of diseases affecting the respiratory system because of the presence of anemia syndrome ^[11,12].

A cross-sectional study that was performed in India with a sample size of 355 participants helped fill in the gap of regional data by reporting a prevalence of 30.7% of anemia of chronic disease (ACD) in the sample which was

significantly higher in males (48.4%) than in females (24%) and the highest prevalence was found in 80+ years old patients (56.5%) [13]. The majority of participants in this study (66%) had mild ACD but the main diseases causing the condition were found to be diabetes (44%), hypertension (39%), and chronic kidney disease (25%) [13]. A study that was done in KEM Hospital, where researchers followed up on 371 heart failure patients, yielded a very high rate of iron deficiency at 50% of patients and a 38% baseline rate of functional iron deficiency [14]. The results of this survey pointed to the connection between iron deficiency and such variables as increased mortality ($p=0.048$) and severe dyspnea ($r^2=0.949$, $p=0.026$), which proved that iron homeostasis and ACD are significant factors determining prognosis in chronic disease patients [13,14].

The IL-6/hepcidin pathway is responsible for the functional iron deficit present in chronic lung disorders, as the destructive effect it has on ferroportin, an iron exporter, limits erythropoiesis and locks iron inside airway macrophages [15,16]. The introduction of IL-6 from the outside leads to the locking of iron in macrophages, which makes bacteria clearing less effective; the value of the sputum hemosiderin index demonstrates a direct relation to frequent severe exacerbations of infections ($\beta = 0.035$, $p = 0.035$) [15]. Such results are achieved by studying India-specific literature: IL-6 and hepcidin levels increase while hemoglobin level decreases significantly [16]. Direct relationship between hepcidin and IL-6 ($r = 0.57$, $p = 0.001$), indirect relationship between hepcidin and hemoglobin ($r = -0.52$, $p = 0.001$). It should be mentioned that the highest median level of hepcidin (55.16 ng/mL) is related to the disturbance of iron transport, which means that even in presence of adequate iron store in the body, inflammation blocks its release [16].

A tertiary-care study in an Indian population comprising 130 chronic pulmonary disease patients indicated that the mean distance walked in 6 minutes was less in tandem with severity of spirometric tests where FEV1 and FVC were found to have a direct correlation with the percent-predicted distance walked in 6 minutes ($P<0.05$) [17]. Post 6-minute walk test PaO₂ was markedly low indicating significant defects in gas exchange [17]. Similarly, in another study done on 30 patients with interstitial lung disease in India, it was concluded that the 6MWD was significantly lower than expected

($p<0.001$) [18]. Following exertion, it was found that oxygen saturation significantly dropped while the pulse, frequency of breathing, and systolic blood pressure increased ($p<0.001$) demonstrating a considerable metabolic shift and increase in cardiopulmonary demand for simple exercise [18]. Taken together, all data indicate that expiratory limitations along with diffusion defects are most likely behind the loss of performance and objective signs of oxygenation [17,18].

Anemia contributes to breathing trouble in patients with chronic lung disorder due to its influence on the oxygen transport capacity and enhancement of inflammation [11]. The Indian population with COPD has shown anemia as an important co-existing condition along with a relation between low hemoglobin level and increased dyspnea class along with worsening clinical status [11]. The chronic inflammatory pathways characterized by the presence of inflammation and resistance to erythropoietin serve to perpetuate a process of chronic anemia [19]. As a result, anemic states negatively affect exercise capacity and leads to the limitation of the activities of patients [11]. In addition, iron malfunction connected with inflammation and inefficiency caused by it result in worsening states of patients [19].

CONCLUSIONS

The study concluded that anaemia was common comorbid condition among people suffering from chronic respiratory conditions and was associated with poor clinical and functional status. Half of the participants were found to be anaemic, and most of them suffered from COPD. Anaemics had low haemoglobin concentrations, more severe dyspnea, higher levels of inflammatory factors (CRP, ESR) and decreased functional exercise capacity than those among non-anaemia patients. The prevalence of anaemia increased with high mMRC dyspnea grades, which revealed the relationship between the low respiratory status and haemoglobin concentration. Overall, the study revealed that anaemia showed reduction in the symptoms, systemic inflammation and decreased physical performance in chronic respiratory diseases.

CONTRIBUTION OF AUTHORS

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Research design – Parashuram, Faseeh K M, Kavya

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