



Prevalence of Anaemia in COPD and Its Association with Smoking

Dr. Pankaj M Gholap¹, Dr. Sushant H Meshram², Dr. Sanket Agrawal³, Dr. Gopalsing Solanke⁴

¹Associate Professor, Department of Respiratory Medicine, GMC, Nagpur.

²Professor and Head of Department of Respiratory Medicine, GMC Nagpur.

³Junior Resident in the Department of Respiratory Medicine, GMC, Nagpur.

⁴Assistant Professor, Department of Respiratory Medicine, GMC, Nagpur.

Conflicts of Interest: Nil

ABSTRACT:

Chronic Obstructive Pulmonary Disease (COPD) is a cause of significant morbidity and mortality throughout the world, being the 4th leading cause of death worldwide. All chronic inflammatory diseases have been known to be associated with Anaemia whereas COPD has been known to be associated with Polycythemia. However recent studies have shown an increased prevalence of anaemia in COPD and it has been attributed to the chronic inflammation associated with the disease. Other factors that might contribute to Anaemia in COPD are malnutrition in severe forms of COPD and the oxidative stress of smoking itself. In this Cross sectional observational study conducted over a period of two years from 2016 to 2018, we have studied the presence of Anaemia in patients of COPD admitted in the ward for acute exacerbation, after excluding cases with other chronic diseases such as Bronchiectasis, Tuberculosis and Carcinoma Lung and also cases of Anaemia related to Haemoglobinopathies. Out of a total of 148 cases of COPD, 107 were included in the study after applying the exclusion criteria and collecting the data from the discharge summaries. We found a total prevalence of anaemia in these COPD cases to be as high as 56% with a prevalence of 62% in males and 37% in females. To find out the association of anaemia with the oxidative stress of smoking in these patients we divided the patients in to one group of active smokers, who had stopped smoking only because of the exacerbation and a group of non-smoker/exsmokers. Only 14 patients were found to be active smokers at the time of admission and of these 9 were anaemic. The odds ratio for active smokers having anaemia was 1.48 (95% Confidence interval ranging from 0.315 to 2.64) showing a significant impact of smoking on the presence of anaemia in COPD patients.

Keywords: Anaemia of Chronic Disease, COPD, Smoking.

INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world¹ but is projected to be the 3rd leading cause of death by 2020. Anaemia is frequently observed

in patients with chronic inflammatory diseases and may negatively affect the cardiovascular status and quality of life.² It is hypothesized that there is a spillover of inflammatory proteins from the lungs to the systemic circulation which leads to the systemic co morbidities in COPD.³ Therefore COPD is theoretically a candidate for Anaemia of Chronic Disease (ACD). Although COPD has been "traditionally" associated with

Polycythemia, recent studies have indicated the presence of anaemia in 7.5 to 23% of COPD patients.⁴⁻⁶

Worldwide the most common risk factor for COPD is tobacco smoking⁷. Several compounds found in cigarette smoke are found to be haematotoxic and smoking in general affects haematopoiesis in a negative way.⁸ Therefore it is also essential to find out the direct contribution of smoking as a causative factor in anaemia in COPD patients. This study therefore was carried out to find out the prevalence of anaemia in COPD and the contribution of smoking in it. The main objectives of the study were as follows:

- 1) To find out the prevalence of Anaemia in COPD cases.
- 2) To find out the prevalence of Polycythemia in COPD cases.
- 3) To find out statistical difference between prevalence of anaemia in smokers with COPD and non smokers/former smokers with COPD with odds ratio.

Materials and Methods

The study was approved by the Institutional Ethics Committee. The study was carried out in a tertiary care hospital in central India. AUTOMATIC BLOOD CELL ANALYSER SYSMEX XS-1000i was used for measurement of Hemoglobin (Hb), Haematocrit and complete blood counts (CBC) in all patients admitted in the department of Respiratory Medicine. A peripheral smear examination was also done to study the red cell morphology. Anaemia was defined as a haematocrit level of <39% in males and <36% in females⁹ or haemoglobin concentration of less than 13.0 g/dL in men and 12.0 g/dL in women as per the WHO definition of Anaemia. A case of COPD was defined with spirometry as per the GOLD guidelines⁷ as having a post-bronchodilator FEV1/FVC<0.70. Data from discharge summaries of COPD patients admitted in the department of Respiratory medicine from August 2016 to April 2018 was studied to collect the data on anaemia and smoking history. Haemoglobin level above 18.5 g/dl in males and 16.5 g/dl in females was considered as polycythemia as per revised 2008 WHO criteria¹⁰. The following patients were excluded from the study with the Exclusion criteria:

- 1) Anaemia of haemoglobinopathies
- 2) Co morbid chronic diseases like Tuberculosis, Carcinoma Lung, Bronchiectasis

Smoking status was defined as follow (Referred from Centers for Disease Control and Prevention; National Health Interview Survey):

- **Current smoker:** An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.
- **Never smoker:** An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
- **Former smoker:** An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview.

Types of Cigarettes

- **Cigarette:** A thin cylinder of ground or shredded tobacco that is wrapped in paper, lit, and smoked.
- **Bidi:** Small, thin, hand-rolled cigarettes. Bidis contain tobacco and can be flavored. When smoked, bidis have higher concentrations of nicotine, tar, and carbon monoxide than conventional cigarettes.

Amount of smoking was calculated using the smoking index in pack years i.e. number of packs of cigarettes smoked per day X number of years of smoking. One pack has 10 cigarettes in India but one pack will be considered as containing 20 cigarettes for calculating pack years for comparative feasibility of the smoking index to other studies. One bidi was considered equivalent to one cigarette for pack year calculation as recommended by Hake SD¹¹ et al in their article on the practical challenges in conducting Respiratory studies.

Percentage prevalence of Anaemia/Polycythemia in COPD was calculated and difference in prevalence of Anaemia amongst smokers and non/ex-smokers with COPD was estimated by using the Odds ratio. Pearson correlation coefficient was used to establish a correlation between smoking index and the level of haemoglobin using Microsoft Excel datasheet calculation tools.

Results and Discussion

A. Prevalence of Anaemia in COPD patients:

After going through the discharge summaries of two years a total of 148 cases of COPD were discovered. After applying the exclusion criteria a total of 107 patients were included in the study. Of the 107 patients included in the study 80 were male and 27 were female. Out of the cases included in the study 60 were found to be anaemic as per the WHO definition of Anaemia giving a prevalence rate of anaemia to be as high as 58% (Fig.1). A similar study by Silberberg DS¹² et al found a very high prevalence of 43.9% anaemic patients amongst Acute exacerbation of COPD patients. The very high prevalence rate of anaemia in our study matches closely with this study probably because both studies have included patients with acute exacerbation of COPD (AECOPD). As we collected data from the discharge summary records of patients admitted in the hospital all the cases included in the study were cases of AECOPD as those included in the study by Silberberg DS et al. In this study they had concluded that Iron deficiency anaemia was very common in cases of COPD but was rarely looked for and treatment of anaemia in COPD cases was found to significantly improve the perception of dyspnoea in the Visual Analogue Scale (VAS).

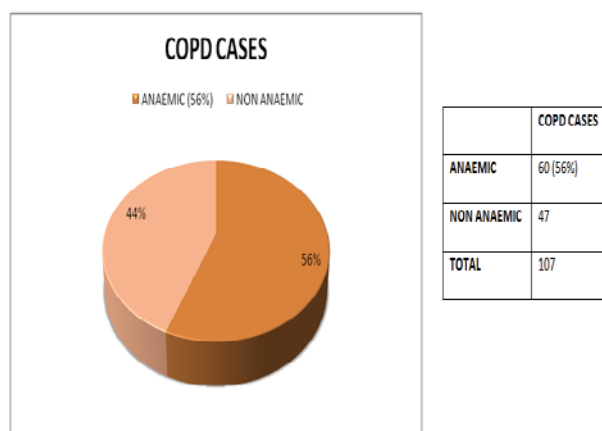


Fig.1: Of a total of 107 cases of COPD included in the study 60(56%) were found to have Anaemia.

This is a very important finding as anaemia can decrease the oxygen carrying capacity of the blood and further aggravate the tissue hypoxia. Normally anaemia is not looked for or treated aggressively in patients of COPD, as COPD has been "traditionally" associated with

polycythemia, and this study may be a wakeup call to do so to significantly improve the dyspnoea in cases of anaemia associated with COPD. The prevalence of Anaemia in our study was much higher than the study conducted by Silberberg DS et al (56% vs. 43.9%) but this can be partially attributed to the fact that the cut off limit for definition of anaemia in their study was 12 g/dl of Haemoglobin for all patients, while we had set a cut off limit of 13 g/dl for male patients and 12 g/dl for female patients. Also the population studied in the study conducted by Silberberg DS et al was a population in a developed country like America while the population studied in our study was a population from a developing country like India with a low socio economic status and high prevalence of anaemia in the general population¹³. All these factors can explain the unexpectedly high prevalence rate of anaemia in the COPD cases that were included in our study as compared to other studies. Few studies have been conducted to study the prevalence of Anaemia in COPD patients. A study by Praveen S et al¹⁴ found a prevalence of 18% of anaemia in COPD cases. In this study both outpatient and inpatient subjects were included in the study. Also the exclusion criteria included in that study were more extensive and comprehensive than those employed in our study. The population included in the study was from Kashmir in Northern India which is a place of relatively high altitude as compared to the place in Central India where our study was conducted. All these factors together may have contributed to the significant difference in the prevalence rate of anaemia in COPD in the two studies. Another study conducted by Park MM et al¹⁵ found a anaemia prevalence of 32% in stable cases of COPD.

Similowski T¹⁶ et al reviewed the literature on the impact of anaemia in COPD and have stressed the need for further studies on the prevalence of anaemia in COPD and its physiological and clinical impact. Our study along with other similar studies points out the fact that the actual prevalence of anaemia in COPD cases might be much higher than previously estimated and most of these cases go undetected or untreated. There is a clear emphasis on actively detecting anaemia in COPD patients and treating it aggressively to

decrease the morbidity and dyspnoea in those patients.

B. Gender wise Prevalence of Anaemia in COPD cases:

Of the total of 107 patients included in our study 80(74.76%) were male and 27(25.23%) were female which is comparable to the study conducted by Park MM et al¹⁵ who found 76% male and 24% female cases of COPD in the study population¹⁵. Of the 80 males in our study 50(62%) males were found to be anaemic as against 10 (37%) females(Fig.2). This shows a slightly higher preponderance of female anaemic patients in our study as compared to the study of Park MM et al¹⁵ which showed 87% male and 13% female anaemic population amongst COPD cases. The higher percentage of anaemic females in our study can be attributed to lower socio economic status and the generally high prevalence of anaemia in the Indian population¹³. None of the females were smokers while only 21(26%) of the males were non smokers. 15(55%) of the Female patients had the risk factor of biomass fuel exposure.

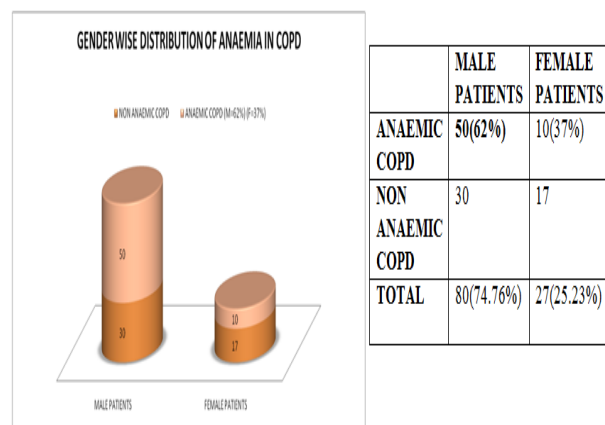


Fig.2: Gender wise prevalence of anaemia in COPD patients.

C. Association of smoking with Anaemia in COPD cases:

Pearson correlation coefficient between the smoking index in pack years and the level of Haemoglobin in COPD patients was calculated to be around -0.096 which is a negative but insignificant correlation.

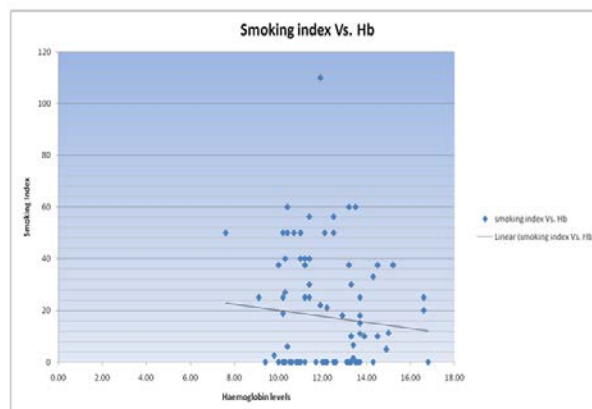


Fig.3: The number of pack years smoked and the Haemoglobin value of COPD patients showed not significant correlation but a slight negative trend indicating a lower Hb level with higher smoking index.

It is clear from the above correlation that simply the smoking index had no correlation with the Hb levels in COPD Patients. This is because most of the patients had already stopped smoking for more than a year and were ex smokers since the onset of the disease and oxidative stress remains for about 12 months after smoking cessation¹⁷.

In order to find out the association of smoking related oxidative stress with the prevalence of anaemia an odds ratio was calculated with Active smoking as the risk factor and Anaemia as the outcome(Fig.4). Non smokers and ex smokers were not considered as a risk factor to be evaluated. A calculated Odds ratio of 1.48 with a 95% confidence interval of 0.315 to 2.64 showed a significant association between anaemia and active smoking.

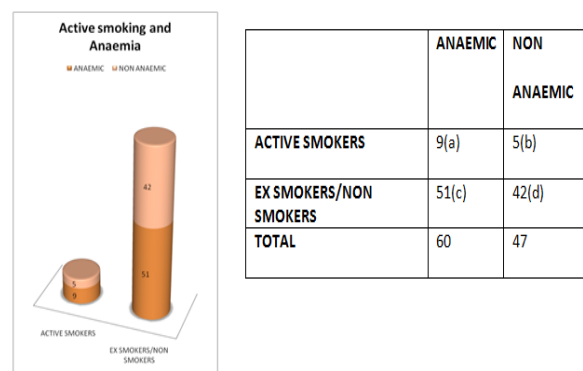


Fig.4: Odds ratio of 1.48 with a 95% confidence interval of 0.315 to 2.64 showed a significant association between anaemia and active smoking.

This finding just highlights the importance of smoking cessation in cases of COPD not only to prevent the accelerated decline in FEV1 but also to prevent the increased co morbidities associated with the oxidative stress of smoking like anaemia. On searching in PubMed and Mendeley desktop software we could not find any similar studies on the association of active smoking with anaemia.

D. Limitations of the study:

The study being a cross sectional observational study no follow could be done to assess the levels of Haemoglobin in the patients of AECOPD after discharge in the stable state. Only indoor patients were included in the study. These patients are admitted because of acute exacerbation and are in increased overall oxidative stress. Stable COPD patients following in the OPD could not be included in the study. Serum levels of Ferritin and percentage saturation of Transferrin was not assessed to find out iron deficiency anaemia and its severity. The population under study was mostly of a lower socio economic status consisting of farmers and labourers who are known to have a high prevalence of malnourishment and anaemia in a country like India. The population studied may not reflect the actual level of anaemia in COPD patients in the general population inclusive of all socio economic strata of the society. As very few such studies have been conducted so far we could not find many references to compare the results of our study with.

Conclusion

COPD is a major public health problem worldwide and is soon going to be the third leading cause of deaths by 2020. COPD can cause systemic inflammation and lead to several co morbidities including anaemia. We found a very high percentage of prevalence of anaemia in COPD cases in our study amounting to 56% with 62% in males and 37% in females. The association between active smoking and anaemia in these patients was significant with an Odds ratio of 1.48 within 95% confidence limits. It is not the pack years of smoking but active smoking that is responsible for causing anaemia. Smoking cessation has the benefit of not just slowing the decline in FEV1 but also in preventing oxidative

stress related co morbidities like anaemia and resultant decreased oxygen carrying capacity of blood giving rise to increase dyspnoea. Active investigation of anaemia in COPD cases can be helpful as the estimated prevalence of anaemia in COPD cases is likely to be higher than previously thought and aggressive treatment of anaemia in such cases can significantly improve the dyspnoea in such patients.

Further large scale multi centric studies need to be done to investigate the prevalence of anaemia in both stable and admitted cases of COPD with a larger sample size representative of all socio economic classes in order to get a more representative picture.

Acknowledgements:

We Would Like To Thank All the Residents in the Department of Respiratory Medicine GMC Nagpur for Helping to Gather the Data and Organising It Especially Dr. Sagar Gandhi, Dr. Sanket Agarwal, Dr. Tauseef Naeem And Dr. Himanshu Apte

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
2. Weiss G, Schett G. Anaemia in inflammatory rheumatic diseases. *Nat Rev Rheumatol* [Internet]. 2013;9(4):205–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23147894>
3. Sinden NJ, Stockley R a. Systemic inflammation and comorbidity in COPD: a result of “overspill” of inflammatory mediators from the lungs? Review of the evidence. *Thorax*. 2010;65(10):930–6.
4. Krishnan G, Grant BJ, Muti PC, et al. Association between anemia and quality of life in a population sample of individuals with chronic obstructive pulmonary disease. *BMC Pulm Med* 2006;6:23.
5. Halpern MT, Zilberberg MD, Schmier JK, Lau EC, Shorr AF. Anemia, costs and mortality in chronic obstructive pulmonary disease. *Cost Eff Resour Alloc* 2006;4:17.

6. John M, Lange A, Hoernig S, Witt C, Anker SD. Prevalence of anemia in chronic obstructive pulmonary disease: comparison to other chronic diseases. *Int J Cardiol* 2006;111(3):365-370
7. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: <http://goldcopd.org>
8. Leifert JA. Anaemia and cigarette smoking. *International Journal of Laboratory Hematology*. 2008. p. 177–84.
9. World Health Organization. Nutritional Anemias: Report of a WHO Scientific Group. In: WHO Technical Report Series 405. Geneva, World Health Organization, 1968; pp. 1–37.
10. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008.
11. Hake SD, Patil ML, Shah TM, Gokhale PM, Suvarna V. Practical challenges in conducting respiratory studies. *Perspect Clin Res*[Internet].2015;6(1):15–9.Availablefrom: <https://www.ncbi.nlm.nih.gov/pubmed/25657898>
12. Silverberg DS, Mor R, Weu MT, Schwartz D, Schwartz IF, Chernin G. Anemia and iron deficiency in COPD patients: prevalence and the effects of correction of the anemia with erythropoiesis stimulating agents and intravenous iron. *BMC Pulm Med* [Internet]. 2014;14(1):2–8. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3946070&tool=pmcentrez&rendertype=abstract>
13. Chellan, R., & Paul, L. (2010). Prevalence of Iron-Deficiency Anaemia in India : Results from a Large Nationwide Survey. *Journal of Population and Social Studies*, 19(2), 59–80.
14. Parveen S, Rangreze I, Ahmad SN, Mufti SA, Khan SS. Prevalence of Anemia in Patients with COPD and Its Potential Impact on Morbidity of COPD Patients. *Int J Clin Med*. 2014;5(8):452–8.
15. Park MM, Durrani M, Zilberberg M: Correlation of severity of anemia with severity of COPD [abstract]. *Am J Respir Crit Care Med*. 2003, 167: A234-
16. Similowski T, Agustí A, MacNee W, Schönhofer B. The potential impact of anaemia of chronic disease in COPD. *Eur Respir J* [Internet]. 2006;27(2):390–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16452598>.
17. Hodge S, Hodge G, Holmes M. et al Increased airway epithelial and T-cell apoptosis in COPD remains despite smoking cessation. *Eur Respir J* 200525447–454