

# Prevalence of anemia and its impact on mortality in patients with acute exacerbation of chronic obstructive pulmonary disease in a developing country setting

*Prevalența anemiei și impactul său asupra mortalității la pacienții cu exacerbare acută a bronhopneumopatiei cronice obstructive într-o țară în curs de dezvoltare*

## Abstract

Chronic Obstructive Pulmonary Disease (COPD) is going to be the third most common cause of death worldwide. The natural course of COPD is interrupted by acute exacerbations (AECOPD) with an overall mortality rate of 10%. Anemia is a well-known independent predictor of mortality in several chronic diseases. Little is known about the impact of anemia on mortality in AECOPD. The aims of this study were to determine the prevalence of anemia in AECOPD patients and its impact on mortality in a developing country setting. We retrospectively studied 200 hospitalized patients with AECOPD (100 died in hospital and 100 survived) in Imam Khomeini teaching hospital, Urmia, Iran. Prevalence of anemia between deceased and surviving patients compared by using x-square test. Mean admission day Hb and Hct level were compared between the two groups by using Student t-test. Anemia was defined according to WHO criteria: Hb < 13 g/dl in males; Hb < 12 g/dl in females. The prevalence of anemia was significantly higher in patients who died in hospital compared to those who survived (72% vs. 49%,  $p=0.001$  and OR= 2.68). The mean  $\pm$  SD Hb level was  $11.5 \pm 2.7$  g/dl among deceased patients vs.  $13.0 \pm 2.0$  g/dl among survivors ( $p$  value < 0.001). The duration of hospitalization was significantly higher ( $p < 0.001$ ) in anemic patients (mean 13.28 days in anemic vs. 7.0 days in non-anemic patients). In bivariate correlation analysis, Hb was positively correlated with FEV1 ( $r=+0.210$ ,  $p=0.011$ ) and negatively with duration of hospitalization ( $r=-0.389$ ,  $p=0.000$ ). Anemia was common in AECOPD patients in this developing country setting and was significantly associated with in hospital mortality.

**Keywords:** Acute exacerbation of chronic obstructive Pulmonary Disease (AECOPD); anemia; mortality, COPD

## Rezumat

Bronhopneumopatia cronică obstructivă (BPOC) va deveni a treia cea mai frecventă cauză de deces din întreaga lume. Evoluția naturală a BPOC este întreruptă de evenimente acute-exacerbări, cu o rată globală a mortalității de 10%. Anemia este un predictor independent, bine cunoscut, al mortalității în mai multe boli cronice. Prea puțin se știe însă despre impactul anemiei asupra mortalității în exacerbarea BPOC. Scopul acestui studiu este determinarea prevalenței anemiei în exacerbările BPOC și impactul ei asupra mortalității într-o țară în curs de dezvoltare. Au fost luați în studiu 200 de pacienți (100 ce au decedat în spital și 100 ce au supraviețuit), spitalizați pentru exacerbare BPOC în Spitalul Universita „Imam Khomeini”, Urmia, Iran. Prevalența anemiei în cele două grupuri (pacienți care au supraviețuit și cei care au decedat) a fost comparată folosind testul x-square. Valoarea medie a hemoglobinei (Hb) și a hematocritului (Ht) la internare în cele două grupuri au fost comparate utilizând testul student. Anemia a fost definită conform criteriilor OMS: Hb < 13 g/dl (sex masculin); Hb < 12 g/dl (sex feminin). Prevalența anemiei a fost semnificativ mai mare la pacienții care au decedat în spital comparativ cu cei care au supraviețuit (72% vs 49%,  $p=0.001$  și OR= 2.68). Valoarea medie a Hb ( $\pm$ SD) a fost  $11.5 \pm 2.7$  g/dl în grupul pacienților ce au decedat vs  $13.0 \pm 2.0$  g/dl în grupul celor care au supraviețuit ( $p < 0.001$ ). Durata spitalizării a fost semnificativ mai mare ( $p < 0.001$ ) la pacienții cu anemie (o medie de 13.28 de zile vs 7 zile la pacienții ce nu erau anemici). În urma analizei prin corelație bivariată, Hb s-a corelat pozitiv cu VEMS ( $r=+0.210$ ,  $p=0.011$ ) și negativ cu durata spitalizării ( $r=-0.389$ ,  $p=0.000$ ). Anemia a fost frecventă la pacienții cu exacerbare BPOC în acest spital dintr-o țară în curs de dezvoltare și s-a asociat cu o mortalitate crescută pe timpul spitalizării.

**Cuvinte-cheie:** exacerbare, anemie, mortalitate, BPOC

Dr. Mohammad Hossein Rahimi-Rad<sup>1,2</sup>, Tannaz Sadighi (stud.)<sup>1</sup>, Masomeh Rabieepour<sup>1,2</sup>, Reza Dinparast<sup>1,2</sup>, Shagayegh RahimiRad (stud.)<sup>3</sup>

1. Faculty of medicine, Urmia University of Medical Sciences, Urmia, Iran

2. "Imam Khomeini" Teaching Hospital, Department of Internal Medicine, Urmia, Iran

3. Faculty of Medicine, Tabriz University of medical sciences, Tabriz, Iran

Corresponding author:

Dr. Mohammad Hossein Rahimi-Rad, Bronchoscopy unit, Imam Khomeini hospital, Ershad avenue, Urmia, West Azerbaijan, Iran (postal code: 57157-81351) E-mail: rahimirad@hotmail.com

**Table 1** Comparison between dead (n=100) and surviving (n=100) patients with AECOPD (n=200)

	Dead patients	Survived patients	Total	P value
<b>Age mean± SD</b>	70.99±10.57	68.23±12.22	69.61±11.48	0.089
<b>Male n (%)</b>	64 (64)	61 (61)	125 (62.5)	0.66
<b>Female n (%)</b>	36 (36)	39 (39)	75 (37.5)	
<b>Smoking yes</b>	62 (62)	66 (66)	128 (64)	0.5
<b>FEV1</b>	39.03±-12.033	42.47±+8.58	41.082±-10.42	0.046
<b>GOLD stage</b>				0.001
II	13 (22.0)	20 (23.0)	33 (22.6)	
III	30 (50.8)	62 (71.3)	92 (63.0)	
IV	16 (27.1)	5 (5.7)	21 (14.4)	
<b>Comorbidity disease**</b>	71 (71)	61 (61)	132 (66)	0.136
<b>Hb g/dl mean± SD</b>	11.6±2.7	13.0±2.1	12.3±2.6	0.000
<b>Hct mean± SD</b>	37.2±8.9	41.2±7.1	39.2±2.5	0.000
<b>Anemic n (%)</b>	72 (72)	49 (49)	121 (60.5)	0.001*
<b>Polycythemia n (%)</b>	6 (3)	8 (4)	14 (7)	0.579
<b>WBC/μL</b>	12310±6843	8809±3872	10551±-5810	0.000
<b>Neutrophil % of WBC</b>	83.85±9.420	73.74±13.32	78.58±_12.64	0.000
<b>Lymphocyte % of WBC</b>	9.01±6.80	16.97±6.80	13.15±-10.25	0.001

**Abbreviations:** GOLD, Global Initiative for Lung Disease, FEV1: forced expiratory volume in 1 s, Hb: hemoglobin, Hct: Hematocrit, WBC: White blood cells

\* Odds ratio=2.68 (CI 1.49-4.81)

\*\* includes diabetes mellitus, hypertension, coronary heart disease, and congestive heart failure

## Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease and is going to be the third most common cause of death worldwide by 2020<sup>1</sup>. Patients with advanced stages of COPD are often hospitalized for acute exacerbation (AECOPD), 10% of them dying during hospitalization and up to one third of the remaining ones die within one year after hospitalization<sup>2</sup>.

It is expected that COPD patients have polycythemia due to smoking and hypoxemia, however studies showed that anemia is more common than polycythemia<sup>3</sup>. Anemia is a well-known independent marker of mortality in several chronic diseases such as, hepatitis C infection, HIV infection<sup>4</sup>, renal failure, malignancy<sup>5</sup>, myocardial infarction<sup>6</sup> and chronic heart failure<sup>7</sup>. There are growing data showing that anemia has negative impact on COPD prognosis, however a Korean study could not find such association<sup>8</sup>.

There are limited information about the relationship between the anemia and mortality in patients with AECOPD, thus in the current study we tried to investigate the relation between anemia and in hospital mortality. We hypothesized that anemia was associated with increased mortality in AECOPD.

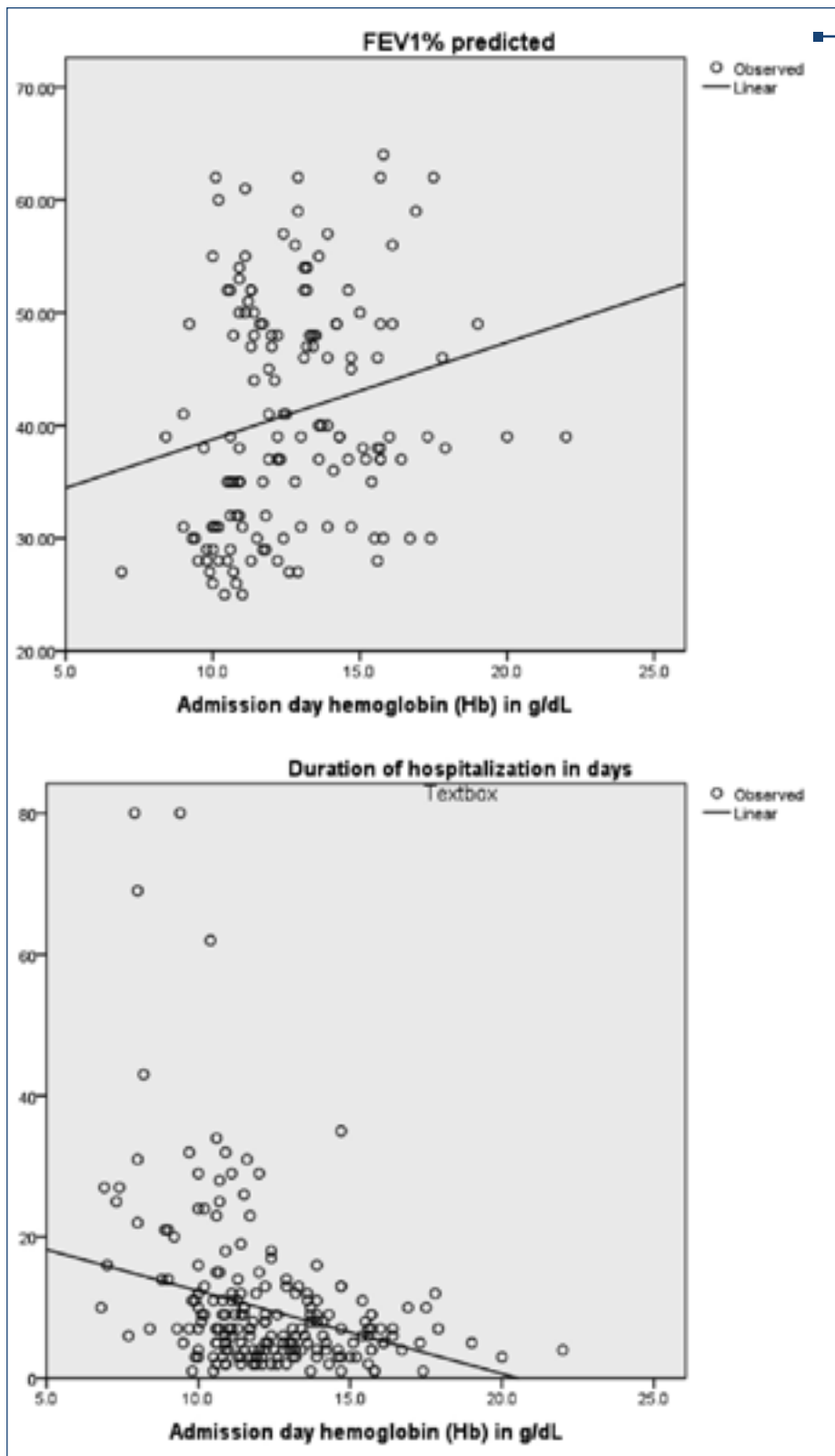
## Materials and methods

This study was done in "Imam Khomeini" Teaching Hospital, Urmia, Iran. We retrospectively studied the hospital charts of 200 patients with initial and final diagnosis of AECOPD (100 died in hospital and 100 were discharged alive from hospital). Patients with a difference between the initial and final diagnosis, patients discharged with their own consent; patients with other comorbidity with well-known anemic consequences such as renal failure, malignancy or absence of cell blood count (CBC) at admission were excluded. Patients hospital's charts were retrospectively reviewed and age, sex, number of days of hospitalization, hemoglobin (Hb) and hematocrit (Hct) levels at admission were recorded.

Anemia was defined according to WHO criteria: Hb < 13 g/dl in males and Hb < 12 g/dl in females<sup>9</sup>. Polycythemia was defined by a Hb >17 g/l in males and >15 g/l in females.

## Statistical analysis

Data were analyzed using SPSS software (IBM, version 19). T-test was used to compare means. X<sup>2</sup>-square was used for comparison of prevalence of anemia and polycythemia between the patients who died and the ones that survived. Correlations between parameters were assessed using bivariate correlation analysis (Pearson Correlation), P value less than 0.05 was considered statistically significant.



**Figure 1.** The bivariate correlation analysis Hb was positively correlated with FEV1 ( $r=+0.210, p=0.011$ ) and duration of hospitalization ( $r=-0.389, p=0.000$ )

## Results

Table 1 shows the comparison of parameters between the two groups of patients. Out of 200 patients, 60.5 % were anemic. The prevalence of anemia among the patients who died was 72% and 49% among patients who were discharged ( $p$  value=0.001 and OR=2.68). Comparing patients who died to those who were discharged, we found significant differ-

ences ( $p < 0,001$ ) in Hb (11.6 vs 13.0 mg/dl) and Hct (37.2 vs. 41.2%). Prevalence of polycythemia was low and not significantly associated with mortality.

The spirometries of 146 patients (59 dead and 87 discharged) were analysed. The other 54 spirometries were either not available, nor have fulfilled ATS/ERS spirometry acceptably criteria<sup>10</sup>.

The duration of hospitalization (Mean± SD) was significantly higher ( $p < 0.001$ ) in anemic patients (13.3±14.3 days) versus non-anemic patients (7.0±5 days). The bivariate correlation analysis showed that Hb was positively correlated with FEV1 ( $r = +0.210$ ,  $p = 0.011$ ) and negatively with duration of hospitalization ( $r = -0.389$ ,  $p = 0.000$ ) (figure 1).

## Discussion

In the current study the prevalence of anemia in patients with AECOPD was 60.5%. Similar to other studies the prevalence of polycythemia was low and not associated with increased mortality. Previous studies have reported a prevalence of anemia ranging from 7.5 to 34% in COPD patients<sup>11</sup>. In a group of 101 COPD patients anemia was diagnosed in 13 patients (prevalence of 13%)<sup>12</sup>. To our knowledge, the prevalence of anemia in the current study is the highest that has ever been reported. The explanation may be that our patients had AECOPD and half of them died during hospitalization (probably more severe/unstable patients). Another possible explanation may be a higher prevalence of anemia in developing countries; most of the previous studies were from developed countries.

The pathogenesis of anemia in COPD patients is probably multifactorial and includes nutritional deficits (vitamin B12, folic acid, iron), chronic stress ulcer, gastrointestinal bleeding, chronic renal failure, concomitant myelodysplastic syndromes, chronic infections and the carboxyhaemoglobin effect of cigarette smoking<sup>13</sup>. Another explanation for higher prevalence of anemia in COPD patients could be their old age.

A growing body of evidence has established that COPD is a chronic inflammatory disease with increased TNF- $\alpha$ , IL-1 and IL-6 which have harmful effects on erythropoiesis<sup>3</sup>. Chronic administration of TNF- $\alpha$  in animals results in anemia, leukocytosis and cachexia<sup>14</sup>.

In the current study anemia had a negative impact on outcome in patients with AECOPD and patients with ane-

mia had a longer duration of hospitalization. The association between anemia and adverse outcomes in COPD is consistent with similar findings in other chronic diseases and other studies in COPD patients. Martinez- Rivera et al. have studied 117 patients hospitalized with AECOPD and reported that mortality risk for patients with anemia was 5.9% within a one year follow up<sup>15</sup>. In a cohort study by Cote et al.<sup>16</sup>, a direct association between hemoglobin levels and mortality of COPD patients was shown. Barba et al.<sup>11</sup> with a study of 289,077 patients with AECOPD reported that anemic patients had a 25% higher risk of re-admission than non-anemic patients. In a study of 283 patients with stable COPD, the prevalence of anemia in chronic disease was 10.24%, with a negative impact on dyspnea and circulatory efficiency during exercise<sup>17</sup>. Chambellan et al.<sup>13</sup> found that each 5% increase in hematocrit was associated with improved survival, which suggests that hematocrit is a strong prognostic predictor of mortality. In another study, the prevalence of anemia in COPD was 33% and annual costs for COPD patients with anemia were more than twice those for patients without anemia (\$17,240 vs. \$6,542,  $p < 0.001$ )<sup>18</sup>.

What is the possible explanation for this impact of anemia on mortality rate in AECOPD? Anemic COPD patients showed an increased inflammatory response compared to non-anemic patients, with elevated erythropoietin levels, suggestive of erythropoietin resistance<sup>12</sup>.

Whether or not the treatment of anemia will result in improvement of functional outcome measures is not determined<sup>14</sup>. Transfusion in anemic COPD patients reduces minute ventilation and the labored breathing<sup>19</sup>.

## Conclusion

Anemia is a common comorbidity in our patients with AECOPD. Anemia was significantly associated with death in hospital. ■

## References

1. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: <http://www.goldcopd.org/>.
2. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest*. 2001;119(4):1190-209.
3. Cavailles A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. *European respiratory review: an official journal of the European Respiratory Society*. 2013;22(130):454-75.
4. Redig AJ, Berliner N. Pathogenesis and clinical implications of HIV-related anemia in 2013. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2013;2013:377-81.
5. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001;91(12):2214-21.
6. Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) Project. *International journal of cardiology*. 2012;154(2):173-9.
7. Karhausen T, Anker SD, Doehner W. Anemia in chronic heart failure—clinical and prognostic significance. *Current medicinal chemistry Cardiovascular and hematological agents*. 2005;3(4):297-303.
8. Joo H, Park J, Lee SD, Oh YM. Comorbidities of chronic obstructive pulmonary disease in Koreans: a population-based study. *Journal of Korean medical science*. 2012;27(8):901-6.
9. World Health Organization. Iron deficiency anemia. assessment, prevention, and control. A guide for programme managers. Geneva, WHO, 2001.
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *The European respiratory journal*. 2005;26(2):319-38.
11. Barba R, de Casasola GG, Marco J, Emilio Losa J, Plaza S, Canora J, et al. Anemia in chronic obstructive pulmonary disease: a readmission prognosis factor. *Current medical research and opinion*. 2012;28(4):617-22.
12. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and inflammation in COPD. *Chest*. 2005;127(3):825-9.
13. Chambellan A, Chailleux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest*. 2005;128(3):1201-8.
14. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *The European respiratory journal*. 2009;33(5):1165-85.
15. Martinez-Rivera C, Portillo K, Munoz-Ferrer A, Martinez-Ortiz ML, Molins E, Serra P, et al. Anemia is a mortality predictor in hospitalized patients for COPD exacerbation. *Copd*. 2012;9(3):243-50.
16. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *The European respiratory journal*. 2007;29(5):923-9.
17. Boutou AK, Stanopoulos I, Pitsioui GG, Kontakiotis T, Kyriazis G, Sichletidis L, et al. Anemia of chronic disease in chronic obstructive pulmonary disease: a case-control study of cardiopulmonary exercise responses. *Respiration; international review of thoracic diseases*. 2011;82(3):237-45.
18. Shorr AF, Doyle J, Stern L, Dolgitsier M, Zilberberg MD. Anemia in chronic obstructive pulmonary disease: epidemiology and economic implications. *Current medical research and opinion*. 2008;24(4):1123-30.
19. Schonhofer B, Wenzel M, Geibel M, Kohler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Critical care medicine*. 1998;26(11):1824-8.