Original Article

A Study of Red Blood Cell Disorders in Chronic Obstructive Pulmonary Disease Patients

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Background: Chronic obstructive pulmonary disease (COPD) is a disease that affecting body systems especially the respiratory system, circulatory system and also hematopoietic system.

Objectives: The primary objective of the present study was to determine the prevalence of anemia and polycythemia in COPD patients. The secondary objectives was to determine factors associated with anemia and polycythemia.

Materials and Methods: The present study was a retrospective study. All medical records of COPD patients visiting the lung diseases clinic of HRH Princess Maha Chakri Sirindhorn Medical Center between January 1, 2016, and December 31, 2019, were reviewed. Complete blood count, biochemistry laboratory results, lung function test, 6-minute walking distance, frequency of exacerbations and admission were recorded.

Results: One hundred twenty-five patients were enrolled. Patients in GOLD stage 1, 2, 3 and 4 were 41.2%, 47%, 9.8% and 2% respectively. Most of the patients were in group A (50.4%). In our study, the prevalence of anemia in COPD patients was 39.2% and none of the patients had polycythemia. There was no association between GOLD classification or group of COPD and anemia. When analyzed by multiple logistic regression, we found that the higher BMI showed a significantly lower risk of anemia than lower BMI (OR 0.877; 95% CI: 0.795 to 0.967) and the frequency of acute exacerbation correlated with anemic condition statistically significant (OR 1.402, 95% CI: 1.142 to 1.721). Anemia and frequency of exacerbation had very low level of positive correlation (r=0.282) at the significance level.

Conclusion: Anemia was common comorbidity in COPD patients. Lower body mass index and frequency of exacerbation were significantly related to anemia.

Keywords: Chronic obstructive pulmonary disease; Anemia; Polycythemia; Hemoglobin

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Chronic obstructive pulmonary disease (COPD) is the most common disease of chronic inflammatory lung disease leading to be the major cause of death in the world population. According to the WHO study, by 2020, COPD will be the 3rd leading cause of death for citizens worldwide[1]. COPD often occurs with emphysema and/or chronic bronchitis causing limitation of airflow within the airway and lung parenchyma[1]. Patients often have many co-morbidities resulting from inflammation mechanisms such as muscle wasting, ischemic heart disease, heart failure, arrhythmia, peripheral vascular disease, hypertension, type 2 DM, metabolic syndrome, osteoporosis, anxiety, depression and anemia[2]. Anemia is common in COPD patients due to the mechanism of red cell production affected by increased cytokines from the inflammatory process which results in the shorter lifespan of red cells and the resistance to erythropoietin (EPO) hormones leading to a decrease in bone marrow hemoglobin production[3]. In addition, inflammation mechanisms encouraging the liver to synthesize more hepcidin proteins, which higher levels of hepcidin proteins will inhibit irons absorption in the intestines and inhibit iron release from the spleen. Besides, some irons were accumulated in the spleen and macrophage causing the decreasing of plasma iron level[3]. Anemia causes inadequate oxygen to support cells thus the patient has a low quality of life. However, patients with COPD will have a chronic hypoxic status which stimulates erythropoietin hormones synthesis and may cause secondary polycythemia[3].

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Hematologic disorders in COPD patients have not been investigated in Thailand. Therefore, the present study had a primary objective was to determine the prevalence of anemia and polycythemia in COPD patients. The secondary objective was to determine factors associated with anemia and polycythemia.

Materials and Methods

Study design and participants

The present study was a 4-year retrospective study at the lung diseases clinic of HRH Princess Maha Chakri Sirindhorn Medical Center, Thailand.

Inclusion criteria

All chronic obstructive pulmonary disease patients, 40 years of age or older visited the lung diseases clinic, HRH Princess Maha Chakri Sirindhorn Medical Center between January 1, 2016, and December 31, 2019.

Exclusion criteria

Patients with other lung diseases besides COPD such as asthma, infectious lung diseases, bronchiectasis.

Patients with autoimmune diseases, cancer, metabolic diseases, hematologic diseases (leukemia, lymphoma, myeloproliferative disorder, pure red cell aplasia, thalassemia, bone marrow disease Heart failure Ischemic heart disease and osteoporosis.

Patients who recently had COPD exacerbation within 3 months.

Patients who were treated with antibiotics and/or corticosteroids for a long time including any treatment that causes low immunity.

Patients who lack follow-up.

Patients with chronic renal disease stage 4 or 5.

Patients without complete blood count results.

Patient with dementia.

The variables used in this study were recorded including gender, age, body mass index (BMI), respiration rate, heart rate, serum hemoglobin, hematocrit, leukocyte, eosinophil, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet, serum albumin, serum globulin, total protein, serum cholesterol, creatinine, glomerular filtration rate (GFR), peak expiratory flow rate (PEFR), post-bronchodilator forced expiratory volume in one second (FEV_1), the 6-minute walk distance (6 MWD), resting O_2 saturation, frequency of exacerbations. Laboratory data will be collected at the nearest time that COPD was diagnosed.

Definition of COPD

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation (post-bronchodilator FEV_1/FVC <0.7) that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development[2].

Definition of anemia

The World Health Organization defines anemia as a hemoglobin level of less than 13 g/dl in males and 12 g/dl in females[4]. Normocytic anemia was defined as MCV of 80 to 100 fL. Microcytic anemia was defined as MCV <80 fL.

Definition of polycythemia

Polycythemia (erythrocytosis) is an abnormal elevation of hemoglobin (Hb) and/or hematocrit (Hct) in peripheral blood. Polycythemia is considered when the hematocrit is greater than 48% in women and 52% in men, and considered when there is a hemoglobin level of greater than 16.5 g/dL in women or hemoglobin level greater than 18.5 g/dL in men[5].

The present study was approved by the ethics committee of Srinakharinwirot University, Thailand (SWUEC/E-221/2562). This study was conducted in accordance with the Declaration of Helsinki. Individual patient data were anonymized and stored in an encrypted computer.

Statistical analysis

The population used in this study was COPD patients who came to the lung diseases clinic of HRH Princess Maha Chakri Sirindhorn Medical Center between January 1, 2016 and December 31, 2019. The sample size was calculated from Crazy and Morgan's formula. The value of Z was set at 1.96. The prevalence of anemia in COPD patients was 7.1[4]. The number of lung disease patients attending the lung disease clinic during that duration was 357 patients. The authors also calculated for a 10% drop-out rate. Thus, the calculated sample size was 88 patients in the present study. However, only 51 patients had a pulmonary function test that was recorded in online medical records. The pulmonary function factors are the major factors that need to be studied. Therefore, we collected all patient hat met the criteria for inclusion and exclusion criteria, with the exceptional the lack of pulmonary function test data. Data was collected from the 125 patients to achieve the most complete information on COPD patients.

All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). In descriptive statistics, by using mean, percentage and standard deviation, Chi-square test multiple logistic regression to test for the relationship of factors affecting hematologic abnormalities. The results are displayed as odds ratio (OR), 95% confidence interval (95% CI), and p-value <0.05 was considered statistically significant. Using the Spearman rank correlation coefficient to find the relationship between anemia and factors contributed to the anemia.

Results

One hundred twenty-five patients were enrolled. Most of the patients were male (92.8%). The mean age of the patients was 72.62±10.44 years. Forty-nine patients (39.2%) had anemia. The total number of mean corpuscular volume (MCV) = 80.97±8.88 fL, which was normocytic anemia (MCV = 80 to 100 fL) 63.27% and microcytic anemia 36.73%. Megaloblastic anemia or polycythemia was not

found. White blood cells and platelets were not found abnormalities also. The patients were categorized (by symptoms and exacerbation history) in group A 50.4%, group B 12.8%, group C 24%, and group D 12.8%. Assessing the severity of the disease using the GOLD classification (post-bronchodilator FEV_1) found GOLD stage 1, stage 2, stage 3 and stage 4 were 41.2%, 47%, 9.8% and 2% respectively. Comparing with anemic and non-anemic group, anemic group had a lower body mass index (p=0.01) and MCV also lower than the non-anemic group (p=0.009) (Table 1).

The peak expiratory flow rate in patients with anemia was lower than non-anemia (p=0.032) and the frequency of acute exacerbation in patients with anemia was higher than non-anemia (p=0.01) (Table 2).

Analyzed by multiple logistic regression, the higher BMI showed a significantly lower risk of anemia than did lower BMI (OR 0.877; 95% CI: 0.795 to 0.967) and the frequency of acute exacerbation was significantly related to anemia with a statistical significance (OR 1.402, 95% CI: 1.142 to 1.721). The GOLD classification or group of COPD was not associated with anemia (Table 3). Spearman's correlation analysis showed that anemia and acute exacerbation had a very low positive correlation at a

Table 1. Baseline characteristics of the patients with COPD (n=125)

Variable	Non-anemia (n=76)	Anemia (n=49)	p-value
Male, n (%)	68 (89.47)	48 (97.57)	0.088
BMI (kg/m^2)	22.61±3.64	20.73±4.26	0.007
Age (years)	71.66±10.97	74.10±9.47	0.235
COPD group, n (%)			0.114
COPD group A	46 (60.53)	17 (34.69)	
COPD group B	9 (11.84)	7 (14.29)	
COPD group C	16 (21.05)	14 (28.57)	
COPD group D	5 (6.58)	11 (22.45)	
GOLD stage, n (%)			0.818
GOLD stage 1	16 (42.11)	5 (38.46)	
GOLD stage 2	18 (47.37)	6 (46.15)	
GOLD stage 3	3 (7.89)	2 (15.39)	
GOLD stage 4	1 (2.63)	0 (0)	
Heart rate (beats/minute)	81.32±12.68	82.94±14.00	0.504
Respiratory rate (breaths/minute)	19.76±1.73	19.55±2.42	0.596
Hemoglobin (g/dL)	13.86±1.71	11.85±1.61	<0.001
Hct (%)	41.23±4.72	35.60±4.75	<0.001
MCV (fL)	84.67±6.66	80.97±8.88	0.009
MCHC (g/dL)	33.49±1.56	32.98±2.20	0.131
RDW (%)	14.01±1.40	14.54±1.79	0.066
Eosinophil (/µL)	4.95±4.41	3.84±4.53	0.176
Leucocyte (/µL)	8,351.05±2644.71	9,702.65±4255.28	0.050
Platelet (/µL)	274,552.63±81539.75	280,530.61±81972.84	0.690
Serum albumin (g/dL)	3.92±0.77	3.84±0.90	0.640
Serum globulin (g/dL)	3.00±0.69	2.90±0.70	0.682
Total protein (g/dL)	5.07±3.26	5.64±2.83	0.301
Creatinine (mg/dL)	1.00±0.24	0.97±0.29	0.593
eGFR ml/min/1.73 m^2	85.97±27.28	91.80±46.58	0.234
Serum cholesterol (mg/dL)	185.76±43.33	187.73±41.22	0.814

Data shown as mean±SD or n (%).
BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = The Global Initiative for Chronic Obstructive Lung Disease; Hct = hematocrit; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; RDW = red blood cell distribution width; eGFR = estimated glomerular filtration rate

Table 2. Physiological findings of patients with COPD (n=125)

Variable	Non-anemic (n=76)	Anemic (n=49)	p-value
PEFR (L/min)	291.43±110.45	247.22±112.93	0.032
6 MWD (m)	300.47±78.64	285.46±75.53	0.437
Frequency of AE (times/year)	0.987±2.16	2.96±3.43	0.001
FEV_1 post-BD (% predicted)	75.12±19.287	72.63±27.53	0.722
FEV_1/FVC post-BD (%)	53.88±17.78	54.68±27.45	0.381
Resting SpO_2 (%)	98.86±1.52	98.63±1.349	0.381

Data shown as mean±SD
PEFR = peak expiratory flow rate; 6MWD = 6-minute walk distance; AE = acute exacerbation; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Post-BD = post-bronchodilator; SpO_2 = peripheral oxygen saturation

Table 3. Independent factors associated with anemia in COPD patients by multivariate logistic regression method (n=125)

Parameter	OR	95% CI	p-value
BMI (kg/m^2)	0.877	0.795 to 0.967	0.009
Frequency of AE (times/year)	1.402	1.142 to 1.721	0.001

BMI = body mass index; AE = acute exacerbation

significant level (p=0.01).

Discussion

According to the study, we found that 39.2% of patients with COPD were anemia and had no polycythemia. Our study is the first study in Thailand that shows prevalence of anemia and polycythemia in Thai COPD patients. These results are compatible with the other researches such as Oh et al studied in Korea found that patients with COPD had a prevalence of anemia 7.1%[6]. Parveen et al[7] and Sarika et al[8] studied in India found that COPD patients had a prevalence of anemia, 18% and 31.6% respectively. Cote et al conducted a study in the United States found that COPD patients had a prevalence of anemia 17% and the prevalence of polycythemia is 6%[9].

In the present study, the prevalence of anemia condition was higher than in other studies, maybe the result of the nutritional status in Thai population in a rural area. In addition, the prevalence of polycythemia was not found probably caused by the small sample size, most of the patients were group A which had less symptom and good oxygen saturation. As Similowski et al review confirmed that the prevalence of anemia was more than polycythemia[10]. According to a recent study by Zhang et al in moderate to very severe COPD, secondary polycythemia was found in 9.2% male and 3.5% female participants[11]. Male sex, current smoking, impaired diffusing capacity for carbon monoxide (DLCO), and severe hypoxemia were associated with increased risk for secondary polycythemia[11]. Continuous or nocturnal supplemental oxygen use were associated with decreased risk for polycythemia[11].

When considering the sample proportion, the majority of the samples in our study were the low-risk group, with 63.2% of COPD group A and group B, and the samples at high risk for COPD group C and D 36.8%. As reported by Mireia Raluy-Callado in 2013, the prevalence of GOLD A and B were 66.4%, GOLD C and D were 33.6%[12].

When comparing the factors affecting anemia, patients with anemia had normochromic normocytic anemia which might be anemia of chronic disease. The cause of anemia is due to the shorter life expectancy of red blood cells and abnormalities in the adjustment of bone marrow function. Furthermore, there are disorders of the metabolism of iron elements that cause iron to accumulate in the RE cell but cannot be used to produce red blood cells. These results were consistent with the explanation of the pathophysiology of anemia in the research of Similowski et al[10].

When considering the factors of body mass index, anemic group had lower BMI than non-anemic group. In accordance with research by Oh et al[6], Sarika et al[8] and Shah Mohammad[13], malnutrition was associated with anemia, however, not found the significance of other nutritional factors studied, such as albumin level or cholesterol levels. This may be the result of too small sample volume, thus not found statistical significance in this study.

Peak expiratory flow rate in the anemic group was significantly lower than non-anemic group. This result was similar to the study of Waseem revealed the presence of

anemia and lower iron status may associate with lower peak expiratory flow rate in asthma patients[14]. In our study, there was no statistical significance in post-bronchodilator FEV1 and post-bronchodilator FEV1/FVC between the two groups. Our study had results similar to Guo et al, but our study did not measure DLCO and cardiopulmonary exercise testing parameters[15]. Decreased oxygen supply to the tissues caused by anemia can result in impaired functioning of the cells which affects organ systems including respiratory muscles.

When comparing factors of the frequency of acute exacerbation, the frequency of acute exacerbation was significantly correlated with anemic conditions. Probably the frequency of acute exacerbation represents the increasing severity of the disease and resulting in more stimulating inflammatory processes in the body, respectively. The results are in relation to the research of Parveen et al[7]. In addition, the study of Begum found that patients with COPD had anemia, which was also a risk factor for death due to acute respiratory failure during the exacerbation of the disease[16].

Analyzed with multiple logistic regression, the higher BMI showed significantly lower risk of anemia than did lower BMI, and the frequency of acute exacerbation significantly correlated with anemic condition. Both BMI and frequency of acute exacerbation are consistent in terms of pathophysiology. The reduced BMI and the catabolic energy state during the acute exacerbation result in forced breathing and stimulating the body to create various cytokines such as TNFα, IL-6 which provoke inflammation throughout the body[17]. The inflammation reduces production and increases resistance to EPO and stimulates the liver to produce more hepcidin hormones. Higher levels of hepcidin inhibit the absorption of iron in the intestines and the release of iron from the spleen. Besides, there is iron accumulation in the spleen and macrophage cells instead, causing the low serum iron level leading to anemia in the end. This corresponds to the explanation of the physiology of anemia conditions in Sarkar et al[18].

Summary

Anemia was common comorbidity in COPD patients, who visited the lung clinic at HRH Princess Maha Chakri Sirindhorn Medical Center. Lower body mass index and the frequency of exacerbation were significantly related to anemia.

What is already known on this topic?

Patients with COPD often have many co-morbidities resulting from inflammation mechanisms such as muscle wasting, ischemic heart disease, metabolic syndrome, osteoporosis, anxiety, depression and anemia.

What this study adds?

The prevalence of anemia in Thai COPD patients was 39.2% and none of the patients had polycythemia. Low body mass index and the frequency of acute exacerbation are associated with anemia. These findings suggest that early detection of anemia and treatment of anemia in COPD patients may be beneficial to improve quality of life.

Research limitations

This research has limitations. Only 51 patients had a pulmonary function test that was recorded in online medical records. There is also information bias, patients received a complete hematologic test at least once a year. The time taken may not be related to the time when diagnosing COPD, which affects the uncertainty in the anemic condition. However, in patients who had complete blood count data more than once, data will be collected at the nearest time COPD was diagnosed.

Suggestion

The study design is a retrospective study leading to incomplete data. A prospective study may be considered or this study may be taken in other lung disease clinics. Moreover, this study may be a guide for conducting experimental research to correct anemia in COPD patients and follow the treatment results and quality of life in the long term.

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Potential conflicts of interest

The authors declare no conflict of interest.

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