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COPD and Erythropoiesis: The Relationship Between Inflammation and Serum Erythropoietin-Prospective Cohort Study

KOAH ve Eritropoez: İnflamasyon ve Serum Eritropoetin Arasındaki İlişki-Prospektif Kohort Çalışması

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ABSTRACT Objective: In our study, we aimed to investigate how respiratory failure and inflammation affect erythropoiesis in chronic obstructive pulmonary disease. **Material and Methods:** The data of 44 patients who adhered to the trial protocol during both the attack and stability phases were assessed. The correlation among blood markers, pulmonary function test [forced expiratory volume in one second (FEV_1)], and erythropoietin (EPO) levels was assessed in patients throughout the attack-stable period and in polycythemic-anemic individuals. **Results:** EPO [14.55 mIU/mL vs. 12.55 mIU/mL (p=0.048)], neutrophil to lymphocyte ratio (NLR) [3.51 vs. 3.91 (p=0.043)], and FEV_1 [1,140.3 mL vs. 996.3 mL (p=0.001)] were elevated throughout the stable phase. C-reactive protein (CRP) [6.6 and 24.35 U/L (p<0.001)] was higher during the attack period. When the parameters of polycythemics in stable and attack periods were compared, hemoglobin [16.38 g/dL, 17.1 g/dL (p=0.019)] and hematocrit [48.77% and 51.61% (p=0.019)] were found to be higher in attack, while FEV_1 [1,244 mL, 640 mL (p=0.001)] was found to be lower. When the parameters of anemia patients in stable and attack periods were compared, NLR [5.78 and 3.94 (p=0.025)] was found to be higher in the stable period. CRP [76.21 U/L and 22.76 U/L (p=0.031)] and EPO [45.75 mIU/mL and 19.63 mIU/mL (p=0.007)] were elevated during the attack period. **Conclusion:** The suppression of EPO levels during exacerbation phases in all patient groups reflects the inhibitory influence of inflammation on EPO synthesis. Although heightened erythropoiesis during the exacerbation phase mitigated FEV1 decline in anemic patients, erythrocyte production was inhibited during the stable phase owing to diminished EPO levels and persistent inflammation. In patients with polycythemia, hemoglobin and EPO levels appear to be less affected by inflammation.

Keywords: Anemia; COPD; erythropoiesis; erythropoietin; polycythemia

ÖZET Amaç: Çalışmamızda, kronik obstrüktif akciğer hastalığında solunum yetmezliği ve inflamasyonun eritropoezi nasıl etkilediğini araştırmayı amaçladık. **Gereç ve Yöntemler:** Çalışma protokolüne uygun 44 hastanın atak ve stabil dönemlerindeki verileri değerlendirildi. Olgularda, atak-stabil dönem ve polisitemik-anemik olanların kan parametreleri, solunum fonksiyon testi [1. saniyedeki zorlu ekspiratuar volüm (forced expiratory volume in one second "FEV_1")] ve eritropoetin (EPO) düzeyleri arasındaki ilişkisi değerlendirildi. **Bulgular:** Stabil dönemde EPO [14,55 mIU/mL ve 12,55 mIU/mL (p=0,048)], nötrofil-lenfosit oranı (NLO) [3,51 ve 3,91 (p=0,043)] ve FEV_1 düzeyleri [1.140,3 mL ve 996,3 mL (p=0,001)] yüksek bulundu. C-reaktif protein (CRP) [6,6 ve 24,35 U/L (p<0,001)] atak döneminde beklenildiği üzere yüksekti. Polisitemiklerin stabil ve atak dönemlerindeki parametreleri karşılaştırıldığında hemoglobin [16,38 g/dL, 17,1 g/dL (p=0,019)], hematokrit [%48,77 ve %51,61 (p=0,019)] atakta yüksek bulunurken, FEV_1 [1.244 mL, 640 mL (p=0,001)] düşük bulundu. Anemi hastalarının stabil ve atak dönemlerindeki parametreleri karşılaştırıldığında stabil döneminde NLO [5,78 ve 3,94 (p=0,025)] yüksek bulundu. Atak döneminde CRP [76,21 U/L ve 22,76 U/L (p=0,031)] ve EPO [45,75 mIU/mL, 19,63 mIU/mL (p=0,007)] yüksek bulundu. **Sonuç:** Alevlenme döneminde tüm hasta gruplarında EPO seviyelerinin düşük olması, inflamasyonun EPO üretimi üzerine baskılayıcı etkisini göstermektedir. Anemiklerde atak döneminde eritropoez artışı FEV1 kaybını engellerken, stabil dönemde EPO düşüklüğü ve kronik inflamasyon nedeniyle eritrosit üretimi baskılanmıştır. Polisitemi hastalarında hemoglobin ve EPO düzeylerinin, inflamasyondan daha az etkilendiği görülmektedir.

Anahtar Kelimeler: Anemi; KOAH; eritropoez; eritropoetin; polisitemi

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by severe and irreversible airway obstruction, leading to high mortality and morbidity and damaging the national economy with long-term drug use and advanced respiratory support.[1]

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Chronic bronchitis and emphysema are considered central to the pathogenesis of COPD, and research has been undertaken on this topic. However, chronic inflammation has become more prominent in the recent period. Studies in this field have shown that the extra pulmonary effects of COPD are related to chronic inflammation. As a proof of this, it has been observed that patients with similar pulmonary function test parameters and radiologically similar findings overestimate the severity of their symptoms.[2,3]

Erythropoietic pathologies are one of the systemic effects of COPD. The conventional view of erythropoiesis abnormalities is that polycythemia is common due to chronic hypoxemia. Recently, however, the traditional belief that the widespread use of long-term oxygen therapy (LTOT) decreases the frequency of polycythemia, and that chronic inflammation causes anemia of chronic disease has begun to lose its place.[3,4]

Polycythemia and anemia can lead patients with COPD to over-experience their symptoms. As a consequence, COPD treatment can be aggressive.[5] The cause of polycythemia in COPD is more clarified compared to anemia. Polycythemia is frequently seen in patients with chronic hypoxemia and smokers. Nevertheless, anemia is more intricate and has various etiologies. In COPD exacerbations, released inflammatory mediators suppress erythropoiesis, while renal failure, malnutrition, low testosterone levels, growth hormone abnormalities, oxygen supplementation, theophylline therapy, angiotensin-converting enzyme inhibition, and aging are recognized as additional factors potentially linked to the onset of anemia.[6]

Erythropoiesis is regulated by erythropoietin (EPO). Hypoxia increases renal synthesis of EPO. Proinflammatory cytokines have been demonstrated to suppress EPO synthesis via influencing the kidneys.[7,8] Studies have yielded varying outcomes regarding COPD and EPO levels. A study indicated that forced expiratory volume in one second (FEV_1) diminished while EPO elevated in mild, moderate, and severe COPD.[8-10] Another study revealed that EPO levels were either normal or diminished in COPD patients.[11]

Consequently, based on our literature assessments, we sought to analyze the impact of inflammation on erythropoiesis by comparing hemoglobin (HGB) and EPO levels with inflammatory markers during exacerbation and stable phases in patients with COPD.

MATERIAL AND METHODS

This is a prospective cohort study that was carried out over a 1-year period, from July 2022-July 2023.The present study was conducted with 44 patients who were evaluated in Kırıkkale University Faculty of Medicine, Department of Chest Diseases Outpatient Clinic and Emergency Department, who were older than 18 years of age, diagnosed with COPD according to GOLD criteria, interned to the Chest Diseases service due to COPD attack and met the inclusion criteria (being older than 18 years of age, not having chronic renal failure, rheumatologic disease, oncologic pathology, diabetes mellitus, cardiac failure, history of blood transfusion and having a diagnosis of COPD). Ethics committee (Kırıkkale University Clinical Research Ethics Committee; date: July 21, 2022; no: 05/01) approval and support from the Scientific Study Project Coordination Unit were obtained. Our study was conducted in accordance with the principles of the Helsinki Declaration. Following the provision of verbal and written information regarding the study, signed informed consent was secured from the patients. The outcomes of standard tests conducted during the diagnosis of a COPD exacerbation, including hemogram [white blood cell, HGB, hematocrit (HCT), neutrophil, lymphocyte values], biochemistry [C-reactive protein (CRP), iron, ferritin, EPO, and FEV_1] values were retrieved from the hospital automation system. Sex, age and LTOT use were evaluated by asking the patients face to face. Patients were categorized into 2 groups: anemia (HGB <13.6 g/dL, HCT <40% for males; HGB <11.9 g/dL, HCT <35% for females) and polycythemia (HGB >16.5 g/dL, HCT >49% for males; HGB >16.0 g/dL, HCT >48% for females). One-month post-discharge, patients were summoned for follow-up, and the identical parameters were reassessed.

DATA ANALYSIS

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was employed to assess

the suitability of the measured variables for normal distribution. A one-way analysis of variance technique was employed to compare these recurrent variables. Mann-Whitney U and Kruskal-Wallis analyses were employed in the absence of normal distribution. Chi-square and Fisher's exact tests were employed to assess the distribution of categorical variables. Descriptive statistics, including median (minimum-maximum) and measures of dispersion, were employed to summarize group comparisons and demographic characteristics. The objective was to illustrate these links through graphical representation. In our study, the threshold for statistical significance was established at $p<0.05$.

RESULTS

The number of patients included in the study was 44. Among these, 7 (15.9%) were female and 37 (84.1%) were male. The mean age of the patients was 68 (52-88) years. Patients were divided into 2 groups as anemia (n=11) and polycythemia (n=9) group. The average age of polycythemia patients was 63 years, whereas that of anemia patients was 68 years. In the polycythemia cohort, all patients were male, but in the anemia cohort, 81.8% were male and 18.2% were female.

Hematological parameters and FEV_1 were assessed in patients during both stable and exacerbation phases. The median EPO levels were significantly higher during the stable phase (14.55 mIU/mL) compared to the exacerbation phase (12.55 mIU/mL, p=0.048). Similarly, neutrophil to lymphocyte ratio (NLR) was higher during the exacerbation phase (3.91) compared to the stable phase (3.51, p=0.043). CRP levels were significantly higher during the exacerbation phase (24.35 U/L) compared to the stable phase (6.6 U/L, $p<0.001$). FEV_1 was significantly lower during the exacerbation phase (996.3 mL) compared to the stable phase (1,140.3 mL, p=0.001) (Table 1).

In the polycythemia cohort, EPO levels did not exhibit a significant difference between the attack and stable phases, although EPO [13.8 mIU/mL-16.23 mIU/mL (p=0.674)] and HGB [17.1 g/dL-16.38 g/dL (p=0.019)] were elevated during the attack phase, respectively. FEV_1 [640 mL-1,244 mL (p=0.001)] levels were found to be significantly higher in the attack. No significant difference was detected in other analyzed values (Table 2, Table 3).

In the anemic patient cohort, EPO levels were considerably elevated throughout both the attack and stable phases (45.75 mIU/mL vs. 19.63 mIU/mL; p=0.007). Nonetheless, the NLR value [3.94-5.78 (p=0.025)], CRP [76.21 U/L-22.76 U/L (p=0.031)], and FEV_1 level [848 mL-1,033 mL (p=0.05)] exhibited significant differences. No significant difference was found in other parameters analyzed (Table 2, Table 3).

TABLE 1: Comparison of blood biochemical markers and FEV_1 values in patients during stable and exacerbation phases

	Median (minimum-maximum)		
Parameters	**Stable phases**	**Exacerbation phases**	**p value**
EPO (mIU/mL)*	**14.55 (1-71)**	**12.55 (2.3-168)**	**0.048**
WBC (10^3 µL)	9.28 (5.08-21.2)	10.62 (4.47-22.6)	0.068
HGB (g/dL)	13.75 (8.5-17.4)	13.7 (7.8-18.5)	0.98
NLR	**3.51 (1.37-13.01)**	**3.91 (1.63-38.94)**	**0.043**
HCT (%)	42.35 (28-54)	41.85 (26.2-56)	0.991
Fe (g/mL)	50 (13-147)	54 (12-234)	0.743
Ferritin (mL/ng)	58.75 (14-1,045)	89.7 (12.5-497)	0.968
CRP (U/L)	**6.6 (0.3-82)**	**24.35 (0.5-268)**	**<0.001**
FEV_1 (mL)	**1,140.3 (156)**	**996.6 (188)**	**0.001**

*The laboratory's normal ranges for EPO are 4-29 mL/mL;
FEV_1: Forced expiratory volume in one second; EPO: Erythropoietin; WBC: White blood cell; HGB: Hemoglobin; NLR: Neutrophil to lymphocyte ratio; HCT: Hematocrit; CRP: C-reactive protein

TABLE 2: Values of polycythemia and anemia patients during the attack period

	Polycythemia patients (n=9) Median	Anemia patients (n=11) Median	
Parameters	**(minimum-maximum)**	**(minimum-maximum)**	**p value**
EPO (mIU/mL)	**8.42 (6-30.3)**	**39.4 (9.75-98)**	**0.003**
WBC (10^3 µL)	13.7 (4.47-16.89)	10.09 (6.06-22.6)	0.412
HGB (g/dL)	**16.8 (16.2-18.5)**	**10.6 (7.8-12.2)**	**<0.001**
NLR	3.84 (2.03-16.73)	3.93 (2.07-7.37)	0.766
HCT (%)	**50.2 (47.1-56)**	**34.3 (26.2-37.4)**	**<0.001**
Fe (g/mL)	**90 (20-234)**	**22 (12-64)**	**0.001**
Ferritin (mL/ng)	166 (26-369)	47 (12.5-497)	0.112
CRP (U/L)	7.6 (1.5-192)	30.5 (0.5-239)	0.331
FEV_1 (mL)	**640 (19-860)**	**830 (450-1610)**	**<0.001**

EPO: Erythropoietin; WBC: White blood cell; HGB: Hemoglobin; NLR: Neutrophil to lymphocyte ratio; HCT: Hematocrit; CRP: C-reactive protein; FEV_1: Forced expiratory volume in one second

TABLE 3: Stable values of polycythemia and anemia patients

Parameters	Polycythemia patients (n=9) Median (minimum-maximum)	Anemia patients (n=11) Median (minimum-maximum)	p value
EPO (mIU/mL)	13 (7-44)	19 (5.9-35.6)	0.23
WBC (10^3 µL)	8.85 (6.71-11.92)	10.41 (5.08-13.4)	0.201
HGB (g/dL)	**16.3 (16.1-17)**	**10.4 (9.2 -12.9)**	**<0.001**
NLR	**2.91 (1.75-6.5)**	**5.17 (2.59-13.01)**	**0.006**
HCT (%)	**48 (47.1-50.9)**	**33.8 (30.6-41.2)**	**<0.001**
Fe (g/mL)	**98 (17-147)**	**31 (17-94)**	**0.02**
Ferritin (mL/ng)	175 (24-264)	51.3 (14-1,045)	0.295
CRP (U/L)	**5.1 (1-14.1)**	**21 (0.3-82)**	**0.031**
FEV_1 (mL)	1,100 (560-2,160)	1,120 (550-1,420)	0.543

EPO: Erythropoietin; WBC: White blood cell; HGB: Hemoglobin; NLR: Neutrophil to lymphocyte ratio; HCT: Hematocrit; CRP: C-reactive protein; FEV1: Forced expiratory volume in one second

Analysis of LTOT utilization among patients revealed that 61.4% employed LTOT throughout the attack phase, whilst 38.6% did not require therapy. Patients with polycythemia exhibited a consistent utilization rate of LTOT at 55.6% during the attack-stable phase, but only 45.5% of patients with anemia employed LTOT during the attack. During the stable period, 72.7% of anemia patients were administered LTOT (LTOT was prescribed and initiated by patients' post-discharge).

DISCUSSION

While it is often accepted that EPO levels are heightened in COPD patients as a result of chronic hypoxia, present study has highlighted diminished EPO production attributable to chronic inflammation. Sharma et al. observed a substantial elevation in EPO levels corresponding to the escalation of illness severity.[12] However, it has recently been suggested that low EPO levels may also be seen in COPD in chronic disease anemia due to chronic inflammation and therefore Rezvani et al. another study showed that EPO levels did not elevate in the advanced stages of COPD.[11] Our study analyzed EPO levels in the same COPD patients during exacerbations and steady phases. We categorized them as anemic and polycythemic and compared blood parameters and FEV_1 levels during attack-stable periods within the groups. In a comparison of EPO values across a cohort of 44 individuals, EPO levels were considerably elevated during the steady phase vs to the attack period. The diminished EPO level during the attack phase, characterized by hypoxia and reduced FEV_1, was noteworthy. This indicates that acute hypoxia alterations have a minimal impact on EPO levels. When EPO levels were categorized into anemic and polycythemic groups, no distinction was observed between the EPO levels of patients in the polycythemic group during stable and attack phases. However, it was noted that the EPO value was significantly elevated in the anemic group compared to the entire patient cohort and during the attack phase relative to the stable phase. The discovery of iron shortage and increased ferritin levels in anemia patients relative to the polycythemic group suggests that the etiology of anemia was anemia of chronic disease. The increased EPO levels in the anemic group, in contrast to the general patient cohort, indicate that it is not attributable to chronic inflammation, but rather a compensatory response to hypoxemia. Several studies have observed an inverse correlation between HGB and EPO, which is an expected finding in erythropoiesis. Under normal conditions, the primary stimuli for EPO production are anemia and hypoxia. However, in our study, as well as in the study conducted by Rezvani et al., no statistically significant relationship was found between EPO and HGB levels.[11] In our results, particularly among anemic patients, no significant correlation was observed between elevated EPO levels and HGB levels. This finding was attributed to low serum iron levels and impaired iron transport due to inflammation in these patients.

Anemia has recently been identified as a comorbidity of COPD.[4,13] Although polycythemia is anticipated in hypoxemic smokers, studies indicate that anemia is more prevalent than polycythemia, with anemia occurring in 12.3% to 23% of cases, compared to 6% for polycythemia.[14,15] Our study revealed a 25% prevalence of anemia, consistent with existing data, however the prevalence of polycythemia was 20%, diverging from the literature. In patients with anemia, as opposed to those with polycythemia, the presence of iron shortage alongside a substantial elevation in EPO levels during the acute phase suggests that erythrocyte formation is heightened in this co-

hort. In patients with polycythemia, decreased EPO levels are thought to be due to feedback suppression of EPO production caused by elevated HGB concentrations. Despite the absence of a significant difference in CRP and NLR values between the 2 groups throughout the attack, the markedly lower FEV_1 values in polycythemic patients indicate that pulmonary function is less compromised in anemic individuals due to heightened erythrocyte production.

Studies indicate that NLR value may serve as a prognostic indicator owing to heightened inflammation in the pathophysiology of COPD, which encompasses inflammatory processes, particularly during exacerbations.[13,16] This study revealed elevated levels of inflammatory markers, including CRP and NLR, in the anemia group, indicating that these patients suffer heightened inflammation during stable periods, while EPO production is repressed, suggesting a link to chronic illness anemia. Elevated NLR and CRP levels indicate that inflammation is more pronounced in anemic patients, which may be associated with anemia. In the comparison of FEV_1 values between the anemic and polycythemic groups, a notable reduction in FEV_1 was evident in the polycythemic group during the attack phase, but it remained relatively constant throughout the stable phase. In this regard, it was demonstrated that polycythemic individuals were less capable of compensating for the reduced FEV_1 compared to the anemic group.

Upon analyzing the utilization of LTOT among patients, it was noted that polycythemic patients employed LTOT more frequently than anemic patients due to their heightened oxygen requirements. The anemic cohort is believed to fulfill this requirement by enhanced erythropoiesis during the acute phase. Nonetheless, no substantial association was identified between LTOT and EPO levels in these patients, indicating the presence of other mechanisms governing EPO regulation.

There were some limitations in our study. The limited sample size was due to the short duration of the study, the high prevalence of comorbid chronic diseases among the patients, and a decrease in the number of patients during the coronavirus disease-2019 pandemic. The study was conducted exclusively on hospitalized patients, excluding those with less severe COPD who did not require hospitalization. Consequently, individuals with low and mild-moderate severity were excluded, precluding any measurement of EPO levels. As the study population consisted exclusively of hospitalized patients, all individuals were categorized under Group E according to the GOLD classification. Moreover, changes observed in pulmonary function tests performed during both exacerbation and stable phases in some patients introduced variability, thereby precluding a consistent evaluation of COPD severity levels. Additionally, further studies with larger cohorts are warranted to more accurately evaluate the relationship between LTOT use, COPD severity, and EPO levels in patients with COPD.

CONCLUSION

It is notable that EPO levels were not high in COPD patients, while EPO blood levels were low during the attack period when hypoxemia was deep. While erythropoiesis is essential for patients with anemia during stable periods, a low level of EPO may indicate inhibition of erythropoiesis in a chronic context. This study highlights the suppressive effect of inflammation on erythropoiesis in patients with COPD, emphasizing the importance of anti-inflammatory treatments in anemic patients.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Elif Kaleli Ercan, Ayşe Füsun Kalpaklıoğlu;* ***Design:*** *Elif Kaleli Ercan, Ayşe Baççıoğlu;* ***Control/Supervision:***

Elif Kaleli Ercan, Ayşe Füsun Kalpaklıoğlu, Ayşe Baççıoğlu; ***Data Collection and/or Processing:*** *Elif Kaleli Ercan;* ***Analysis and/or Interpretation:*** *Elif Kaleli Ercan, Ayşe Füsun Kalpaklıoğlu;* ***Literature Review:*** *Elif Kaleli Ercan, Ayşe Baççıoğlu;* ***Writing the Article:*** *Elif Kaleli Ercan, Ayşe Füsun Kalpaklıoğlu;* ***Critical Review:*** *Ayşe Baççıoğlu, Ayşe Füsun Kalpaklıoğlu;* ***References and Fundings:*** *Kırıkkale University Faculty of Medicine Scientific Research Project;* ***Materials:*** *Elif Kaleli Ercan.*

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