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Anemia and Survival in Chronic Obstructive Pulmonary Disease: A Dichotomous rather than a Continuous Predictor

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Key Words

Anemia · Chronic obstructive pulmonary disease · Forced expiratory volume in 1 second

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a disorder characterized by high mortality. Hemoglobin (Hb) concentration has a prognostic impact on COPD patients receiving long-term oxygen treatment, but its value as an independent predictor of survival among stable COPD outpatients has not been fully clarified by previous studies. ***Objectives:*** To investigate the potential association between anemia and survival in a cohort of stable COPD outpatients. ***Methods:*** A cohort of stable COPD patients, who had had their first spirometry, blood count and serum chemistry profile done between October 1999 and November 2010 were retrospectively analyzed. Patients with heart failure, renal impairment, malignancy, recent hemorrhage and other causes of anemia were excluded. Variables that were found to be univariately associated with survival entered a multivariate stepwise Cox regression analysis model, to allow independent predictors of survival to be identified. ***Results:*** Of 294 patients (67.9 ± 9.8 years old, 64.6% male) 15.6% were anemic (Hb <13 g/dl). The median survival differed significantly between anemic [68.7 (18.1–91.5) months] and nonanemic [79.8 (57.5–98.4) months, p = 0.035] individuals. Independent predictors of mortality in the total population were anemia [hazard ratio (HR) 1.87, 95% confidence interval (CI) 1.06–3.29], age (HR 1.08, 95% CI 1.04–1.12) and forced expiratory volume in 1 s (FEV_1) % predicted (HR 0.94, 95% CI 0.92–0.97); the Hb concentration was neither univariately nor multivariately associated with mortality. ***Conclusion:*** This is the first study to indicate that anemia (but not the Hb value) is independently associated with survival in stable COPD outpatients. It would be better to treat this as a categorical variable in future scoring systems.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide, with increasing prevalence and high morbidity and mortality [1, 2]. Several parameters, both pulmonary and extrapulmonary, such as forced expiratory volume in 1 s (FEV_1), exercise capacity, daily physical activity, severity of dyspnea, body mass index (BMI) and quality-of-life measures have been used previously to predict survival [3–6].

Among extrapulmonary manifestations, anemia, a well-known manifestation of chronic illness [7], could be present among patients with COPD. Prior studies have reported a prevalence of anemia ranging from 7.5 to 21% in COPD populations of varying severity [7, 8]. The clinical impact of anemia is significant; it has been associated

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Table 1. Demographic and clinical characteristics of the total COPD population

	Total population (n = 294)
Gender	
Male (%, n)	64.6 (190)
Female (%, n)	35.4 (104)
Age, years	67.9 ± 9.8
BMI	24.7 ± 5.6
Hemoglobin, g/dl	14.5 ± 1.5
MCV, fl	92 ± 5.8
MCH, pg/cell	31 ± 2.3
FEV_1, % predicted	36.1 ± 18
FVC, % predicted	82.1 ± 21
pO_2, kPa	9.1 ± 1.3
pCO_2, kPa	5.19 ± 0.80
H^+, nmol/l	37.09 ± 3.53
Smoking status	
Current smoker, %	21.1
Ex- or never-smoker, %	78.9
LTOT, %	12.9

pCO_2 = Carbon dioxide partial pressure; pO_2 = oxygen partial pressure.

with increased dyspnea, reduced exercise capacity, higher costs of care and increased morbidity in COPD patients [3, 7, 9, 10].

The association between anemia and increased mortality has been repeatedly reported in various chronic diseases, such as renal failure [11], chronic heart failure [12] and cancer [13]. Although hematocrit value was associated with survival in a large cohort of COPD patients receiving long-term oxygen treatment (LTOT) [14], data from studies conducted among stable COPD patients are few and have not indicated a definite impact of anemia on their prognosis [3]. Against this background, we conducted a retrospective study in order to investigate the putative association between anemia and survival in a cohort of stable COPD outpatients.

Methods

Study Population

Our cohort consisted of stable COPD outpatients who had had their first forced spirometry, full blood count and serum chemistry profile conducted between October 1999 and November 2010. Data were extracted from the hospital's clinical COPD database. The diagnosis of COPD was confirmed by the presence of an FEV_1 to forced vital capacity (FVC) ratio of <0.7 after bronchodilation [15]. All patients were clinically stable and received appropriate treatment for COPD. Patients who had asthma (defined as an increase of ≥12% or ≥200 ml over the baseline value after the administration of a bronchodilator) [16], chronic heart failure (New York Heart Association Class III or IV), renal impairment [estimated glomerular filtration rate (e-GFR) <60 ml/min/1.73 m^2], a history of malignancy, recent gastrointestinal or other hemorrhage, hematologic disorders, inflammatory bowel disease and systemic or autoimmune disorders, were excluded.

Study Design

Data were retrospectively analyzed. For the patients in whom blood analysis and forced spirometry were not conducted at exactly the same time, the pulmonary function testing parameters closest to (within 12 months) the hemoglobin (Hb) measurement were entered into the analysis. Hb concentration measured during pulmonary function testing was not accepted for any of the patients. Anemia was defined as the presence of Hb concentration <13 g/dl for both males and females [3], since the use of a lower threshold (<12 g/dl) to define anemia in postmenopausal women is an issue which is still under debate [17]. Polycythemia was defined by the presence of Hb concentration >17 g/dl in males and >15 g/dl in females. Due to the lack of any significant differences both in baseline characteristics and in outcomes between polycythemic and normocytic patients, they together formed the group of nonanemic patients. Survival data for all participants were available until May 2011. The Brompton Harefield and NHLI Research Ethics Committee ruled that ethical approval is not required for the retrospective analysis of routinely collected clinical data.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 17 for Windows XP. Data are presented as mean value ± 1 standard deviation (SD) or as mean percent predicted value ± 1 SD. e-GFR was calculated from the serum creatinine measurement with the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study [18]. The Kolmogorov-Smirnov test of normality was used to assess the normality of the distribution of variables. Differences between anemics and nonanemics and between survivors and nonsurvivors in demographic data, FEV_1 % predicted, FVC % predicted, the presence of anemia and the Hb concentration were tested utilizing either the Student t test or a χ^2 model. The variables which were found to be univariately associated with survival were then entered in a multivariate stepwise Cox regression analysis model. Corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each independent predictor. The Kaplan-Meier method was used to calculate median survival (with the corresponding 95% CIs) and the overall survival rates. A level of $p < 0.05$ was considered significant.

Results

Study Population

From a total of 707 COPD outpatients, 294 stable patients (190 or 64.6% male and 104 or 35.4% female) were included in the analysis (table 1). Anemia was present in 46 (15.6%) patients and polycythemia in 30 (10.2%). In the nonanemic group, when comparing normocytic and

Table 2. Demographic and clinical characteristics of anemic and nonanemic patients

	Anemic (n = 46)	Nonanemic (n = 248)	p value
Gender			
Male, %	41.3	69	<0.001
Female, %	58.7	31	
Age, years	72.4 ± 10	66.8 ± 9.6	<0.001
BMI	25 ± 6.3	24.7 ± 5.4	n.s.
Hb, g/dl	12.2 ± 0.9	15 ± 1.2	<0.001
MCV, fl	91.4 ± 7.4	92.2 ± 5.5	n.s.
MCH, pg/cell	30.8 ± 3.2	31.2 ± 2.1	n.s.
FEV_1, % predicted	34.2 ± 15.1	36.5 ± 18.5	n.s.
FVC, % predicted	76.7 ± 19	83.2 ± 21.4	n.s.
pO_2, kPa	8.8 ± 1.7	9.2 ± 1.3	n.s.
pCO_2, kPa	5.2 ± 1	5.2 ± 0.8	n.s.
H^+, nmol/l	37.1 ± 3.2	37.1 ± 3.6	n.s.
Smoking status			
Current smoker, %	10.7	23.8	n.s.
Ex- or never-smoker, %	89.3	76.2	
LTOT	28.3	11.7	<0.001

n.s. = Not significant; pCO_2 = carbon dioxide partial pressure; pO_2 = oxygen partial pressure.

Table 3. Demographic and clinical characteristics of survivors and nonsurvivors

	Survivors (n = 223)	Nonsurvivors (n = 71)	p value
Gender			
Male, %	67.3	56.3	0.094
Female, %	32.7	43.7	
Age, years	66 ± 9.8	72.3 ± 8	<0.001
BMI	25.3 ± 5.4	22.9 ± 5.6	0.002
Hb, g/dl	14.6 ± 1.4	14.3 ± 1.6	0.091
MCV, fl	91.8 ± 5.8	92.7 ± 5.9	0.247
MCH, pg/cell	31.6 ± 2.3	30.8 ± 2.4	0.489
FEV_1, % predicted	39 ± 19	27 ± 9.9	<0.001
FVC, % predicted	84.7 ± 21.4	74.3 ± 18.2	<0.001
pO_2, kPa	9.3 ± 1.3	8.7 ± 1.3	0.008
pCO_2, kPa	5.2 ± 0.7	5.2 ± 1	0.813
H^+, nmol/l	37.1 ± 3.6	37 ± 3.4	0.918
Anemia, %	12.6	25.4	0.010
Polycythemia, %	9.9	11.3	0.734
Smoking status			
Current smoker, %	22	16.7	0.560
Ex- or never-smoker, %	78	83.3	
LTOT, %	10.1	13.1	0.091

pCO_2 = Carbon dioxide partial pressure; pO_2 = oxygen partial pressure.

polycythemic patients, the latter were more often female (70 vs. 25.7%, $p < 0.001$) and presented with higher Hb levels (16.4 ± 1.1 vs. 14.8 ± 1, $p < 0.001$); no other differences were noted. The demographic and clinical characteristics of the anemic and nonanemic groups are presented in table 2.

The mean Hb level for anemic patients was 12.2 ± 0.9 g/dl and 15.0 ± 1.2 g/dl ($p < 0.001$) for nonanemic patients. About 17% of the total patient population received LTOT; those prescribed LTOT presented with lower Hb levels than those without it (13.9 ± 1.7 vs. 14.6 ± 1.4, $p = 0.02$). Anemic patients were older, more often females and a higher percentage of them received LTOT when compared to the nonanemic ones. No difference was noted in pulmonary function testing parameters, arterial oxygen tension on room air and BMI between the 2 groups.

Mortality

The mean follow-up duration for the whole population was 32.6 ± 26.9 months and did not differ between anemic and nonanemic patients (32.7 ± 30.7 vs. 32.6 ± 27.4 months, $p = 0.979$). Median survival for the total population was 78 months and survival rates at 3 and at 5 years (all-cause mortality) were 0.78 and 0.66, respectively. Both median survival and survival rates differed significantly between anemics and nonanemics; median survival was 68.7 (18.1–91.5) months for the anemic and 79.8 (57.5–98.4) months for the nonanemic patients ($p = 0.035$), while survival rates at 3 and 5 years were 0.65 and 0.52 for the anemic and 0.8 and 0.68 for the nonanemic group, respectively.

Table 3 presents the differences in patient characteristics between survivors and nonsurvivors. Survivors were younger ($p < 0.001$), presented less frequently with anemia ($p = 0.01$) and had higher BMI ($p < 0.001$), FEV_1 % predicted ($p < 0.001$), FVC % predicted ($p < 0.001$) and arterial oxygen partial pressure on room air ($p = 0.008$), compared to nonsurvivors. Importantly, although anemia predicted death, Hb level did not, nor did gender ratio, mean corpuscular (erythrocyte) volume (MCV), mean corpuscular Hb (MCH), smoking status, treatment with LTOT or the presence of polycythemia.

When these univariate predictors of survival were entered in the multivariate model, the only parameters that were independently associated with mortality in the total population were anemia (HR 1.87, 95% CI 1.06–3.29), age (HR 1.08, 95% CI 1.04–1.12) and FEV_1 % predicted (HR 0.94, 95% CI 0.92–0.97). Figure 1 presents the Kaplan-Meier survival curves for anemic and nonanemic patients, adjusted for age and FEV_1 % predicted.

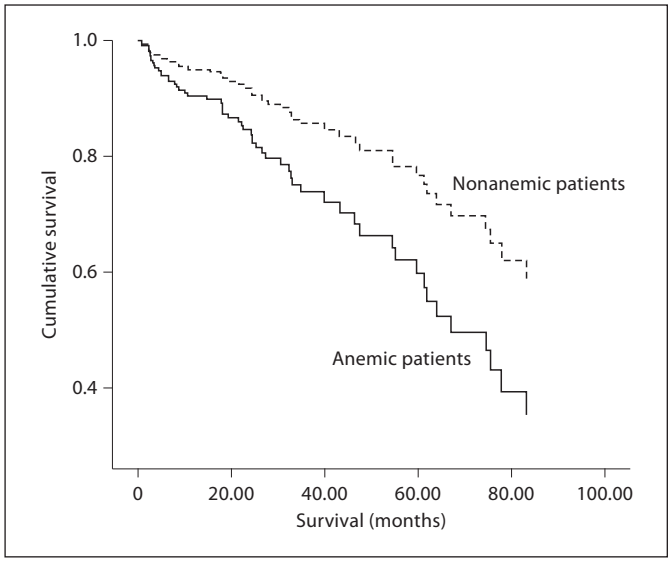

Fig. 1. Survival curves for anemics and nonanemics, adjusted for FEV_1 % predicted and age.

Discussion

In this study, just over 15% of stable COPD outpatients were anemic, and the presence of anemia, along with FEV_1 and age, was a predictor of survival. Polycythemia, with a prevalence of 10%, was less frequent in our patient population and had no impact on mortality. Importantly, Hb levels (when treated as a continuous variable) were not associated with survival, suggesting that anemia is a dichotomous variable. This observation is relevant for investigators who wish to incorporate it into future prognostic stratification systems.

Data on the impact of hematocrit value on COPD survival are few and research in the field is still ongoing. However, our cohort extends prior observations that anemia is an unwelcome feature in COPD. The most important piece of evidence comes from the study of Chambellan et al. [14], derived from the French respiratory home care network, the ANTADIR (Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire Chronique). In this study, anemia was present in 12.6% male and 8.2% female COPD patients who were receiving long-term oxygen therapy; anemic patients had a higher hospital admission rate, a longer hospital stay and a higher mortality rate than nonanemic patients. The multivariate regression analysis identified hematocrit as a major, independent predictor of morbidity and mortality in this population, with the 3-year rate of survival decreasing with lower hematocrit values [9, 14].

However, other studies in the field, which included a general COPD population, have yielded less definite associations between anemia and survival. In the study of Halpern et al. [7], which used data from the US Medicare Claims database, anemia was found among 21% of COPD patients and was an independent predictor of mortality and of increased costs of care. Nevertheless, data on pulmonary function testing were not available for these patients, so the impact of anemia could not be assessed independently of the severity of airflow obstruction. In another study by Cote et al. [3], the prevalence and impact of anemia on survival was evaluated in a cohort of stable COPD outpatients. Although anemic patients had a lower median survival than the nonanemic ones, anemia was not identified as an independent predictor of survival. Our study is the first to identify that the presence of anemia is significantly associated with the survival of stable COPD outpatients, independent of age and FEV_1 % predicted.

Disease burden is usually higher in anemic patients. In most of the previous studies which investigated the clinical impact of anemia in COPD, anemic patients were older, had more severe airflow obstruction and more comorbidities and presented with significantly impaired functional capacity, compared to nonanemic patients [3, 8, 10, 14]. Our study confirms this. Although pulmonary function testing parameters were similar between the 2 groups, anemic patients were older and received LTOT in higher percentage than the nonanemic group. In COPD patients, anemia could either be an epiphenomenon, identifying sicker patients [3], or a true manifestation of chronic immune activation [19–21] resulting in anemia of chronic disease [10] via the impairment of iron homeostasis and the bone marrow response to erythropoietin [22, 23]. In any case, our study indicated that the presence of anemia is of clinical importance, since it is a significant prognosticator of survival in steady COPD outpatients.

The cause of anemia was not apparent from our data, but the observation that MCV and MCH in the anemic patients did not differ from those who were not anemic suggests that anemia of chronic disease was likely the cause. For this proposition to be a truly categorical rather than a continuous variable, evidence would be required of a subset behavior in COPD. In fact, such evidence is available: Garcia-Aymerich et al. [24] recently reported a subtype of patients with milder disease (judged by spirometry), but more frequent exacerbations.

Several studies in the literature have reported an association between smoking and Hb levels. Both hemato-

crit and Hb values are higher in smokers [25, 26], and a positive correlation has been found in women between the number of cigarettes per day and Hb [26]. In our study, the percentage of smokers was higher among the nonanemic patients compared to the anemic patients and among survivors compared to nonsurvivors, but none of these differences reached statistical significance. Nevertheless, smoking cessation has long been proposed to be one of the most important interventions to increase survival in all COPD stages [27]. Future studies are needed in order to independently assess the effect of anemia and smoking status on COPD survival.

Polycythemia was present in approximately 10% of COPD patients in this study. This is slightly higher than the percentage found in other recent studies (range 6–8.3%) [3, 14], possibly reflecting the status of our institution as a tertiary referral centre. It has been reported that the use of LTOT results in the control of polycythemia in patients with COPD [28], but in our study (compared to previous ones) a relatively low percentage of COPD patients (approx. 13%) received LTOT; this could also explain the higher prevalence of polycythemia. Consistent with a prior report [29], the presence of high hematocrit values was not associated with higher mortality.

The correction of anemia has proven beneficial in several chronic disease states. Hb normalization is associated with improved exercise capacity, functional status and quality of life in chronic heart failure and chronic kidney disease [30, 31], and it can decrease morbidity and mortality in patients with renal failure [32]. However, there are no published data on the potential longitude effects of anemia treatment on the functional status or survival of COPD patients. Erythropoietin resistance and increased levels of inflammatory mediators seem to be of major importance for the manifestation of anemia in patients with COPD [33, 34]. Since the therapeutic approach of the anemia of inflammation remains controversial [22], randomized controlled studies are necessary to investigate whether these patients will benefit from erythropoietin administration, iron supplementation or anti-inflammatory drugs.

The careful exclusion of patients with renal impairment and other diseases that could be associated with anemia strengthens our results. Utilizing the MDRD equation, Incalzi et al. [35] recently demonstrated that 20.8% of a population of elderly COPD outpatients presented with normal serum creatinine and low (<60 ml/min/1.73 m^2) e-GFR, and another 22.2% presented with high serum creatinine and low e-GFR. Given the fact that renal failure is a major comorbidity which could contribute to both anemia developing and increased mortality [11, 36], any study on the prevalence and impact of anemia in COPD should take this complication into consideration. Unlike previous studies in the field [3, 33], we were able to exclude patients with renal insufficiency.

The retrospective design we followed limits the results we obtained because it is subjective to the general bias of this kind of methodology. For several patients, the measurement of pulmonary function testing values was not conducted on exactly the same day as the Hb measurement; we tried to minimize the effect of randomly collected spirometric values by choosing the one closest to the Hb measurement. Nevertheless, most of the relevant studies in this field have used a retrospective design [3, 7, 9] with comparable results. The sample size of our study was smaller than that of the ANTADIR, where the relationship between survival and hematocrit was found to be linear. The ANTADIR study included a nongeneral COPD population with respiratory failure and severe comorbidity, so it is possible that the potential impact of anemia as an indicator of disease severity could not be clearly established in that population. Furthermore, the impact of lung volumes, diffusing capacity and physiological measurements, such as the 6-minute walk distance test, were not assessed. These measurements, however, were not conducted at every patient visit, while data on simple spirometry were all available and thus entered the analysis, in order the results to be comparable for the total patient population. Finally, iron levels and erythropoietin concentration were not measured, since they were not included in the regular biochemical testing protocol of COPD outpatients.

In conclusion, this study has indicated that anemia, together with age and FEV_1 % predicted, is a predictor of survival in stable COPD outpatients. However, neither polycythemia nor Hb value (when treated as continuous variables) was found to be associated with mortality. This indicates that if used in a scoring system, anemia should be used as a categorical rather than a continuous variable.

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