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ORIGINAL RESEARCH

The Impact of Anemia on Long-Term Mortality in Hospitalized Patients with Exacerbation of Chronic Obstructive Pulmonary Disease

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Purpose: Anemia is a risk factor for mortality within the general population and is notably prevalent among individuals with chronic obstructive pulmonary disease (COPD). Our objective was to investigate the impact of anemia on the long-term mortality risk of hospitalized COPD patients. Additionally, we aimed to identify the cause of mortality to assess whether it was different in relation to the presence of anemia.

Patients and Methods: This was an observational retrospective analysis of prospectively collected data of consecutive patients admitted because of COPD exacerbation. Clinical characteristics, the presence of anemia, months of survival and cause of death if occurred, were recorded. Patients were categorized into two groups: anemic (for women hemoglobin level < 12 g/dL and for men hemoglobin level < 13 g/dL) and non-anemic. Survival analysis was conducted using Kaplan-Meier curves and Cox proportional hazard regression analysis.

Results: A total of 125 patients (20% women) were included in the study. Among them, 31 (25%) were identified as anemic, By the conclusion of the study, 59 patients (47%) had died: 27 out of 31 anemic patients (87%) and 32 out of 94 non-anemic patients (34%) (p<0.001). Anemia was a robust predictor of mortality one year after admission (adjusted hazard ratio HR; 5.20 [1.86–14.55]); three years after admission (HR 4.30 [2.03–9.10]), and at the study's termination (with a follow-up period ranging from a minimum of 38 months to a maximum of 56 months) (HR; 3.80 [1.96–7.38]). Mortality in the group of patients with anemia was of 27 individuals (87%) and 32 (34%) in patients without anemia (p<0.001). The causes of mortality in patients with or without anemia were similar.

Conclusion: The detection of anemia upon admission for COPD exacerbation serves as a robust predictor of mortality in the subsequent years.

Keywords: anemia, COPD, hospitalization, mortality, prognosis

Introduction

It is well-established that patients with Chronic Obstructive Pulmonary Disease (COPD) have a elevated risk of mortality compared to the general population, with severity of the disease at diagnosis correlating with this risk.[1] Exacerbations of COPD, in terms of both frequency and severity, have also been linked to heightened mortality rates in these patients.[1] A recent meta-analysis concluded that significant predictors of mortality in COPD include prior hospitalization, early readmissions, cardiovascular comorbidity, age, male sex, and the use of home oxygen therapy.[2] Various multifunctional indices have been developed to predict mortality in COPD patients;[3] however, the mortality prediction models developed thus far have only demonstrated moderate discriminative capability.[2]

It is recognized that anemia represents a risk factor for mortality across the general population, irrespective of age, gender, or cardiovascular disease history,[4] and anemia is notably prevalent among individuals with COPD, with prevalence rates ranging from 5% to 38%.[5,6] However, despite its significance, this characteristic has not been incorporated into mortality prediction models for COPD.

There is compelling evidence linking the presence of anemia to an elevated risk of mortality in patients with COPD. As early as 1973, Kilburn and Asmundsson[7] reported that anemia was associated with increased mortality in this disease. Low hemoglobin levels in stable-phase COPD patients are associated with increased healthcare resource utilization, worse quality of life, older age, male gender, and serves as a prognostic predictor for the risk of hospitalization, as well as early and long-term mortality.[5,8,9] Additionally, in patients hospitalized for COPD, the presence of anemia has been associated with adverse outcomes and an increased healthcare burden.[10] However, the mortality risk associated with anemia in patients hospitalized for COPD exacerbation has received scant attention. Existing studies have typically focused on specific time periods or patient characteristics.[11–13] Given that patients with COPD requiring hospital admission represent those with the highest mortality risk, exploring predictive variables in these patients holds particular significance.

We aimed to analyze the impact of anemia on the mortality risk of consecutive COPD patients who required hospitalization due to exacerbation of their disease. Additionally, we aimed to identify the cause of mortality in these patients to assess whether it differs between COPD patients with and without anemia.

Materials and Methods
Study Design and Population
This was an observational retrospective analysis of prospectively collected data from patients consecutively admitted to the Pulmonology ward between July 2019 and December 2020 for acute exacerbation of COPD. The follow-up deadline was February 29, 2024, ensuring a minimum follow-up of 3 years at the time of data analysis.

The diagnosis of COPD was based on age ≥40 years, current or past smoking history (≥10 pack-years), and post-bronchodilator FEV1/FVC <70%. When patients required more than one admission during the inclusion period, only the data from the first admission were recorded.

Patients with concurrent cancer or interstitial lung disease were not included. Those patients who could not be followed up during the established period were excluded.

Data Collection and Measurements
Upon admission, the following variables were recorded: age, gender, body mass index (weight [kg]/height^2 [m]) (BMI), smoking history, spirometric values, number of hospitalizations and emergency department visits in the previous year, and duration of hospital stay. Baseline dyspnea (in stable condition) was assessed using the modified Medical Research Council scale (mMRC)[14] and comorbidity was evaluated using the modified Charlson comorbidity index.[15]

Hematological parameters were measured using the first blood sample obtained for routine clinical testing. Patients were categorized into two groups based on hemoglobin (Hb) levels, classified as anemic and non-anemic. Anemia was defined according to World Health Organization (WHO) criteria: Hb < 12 g/dL for women and Hb < 13 g/dL for men.[16] Anemia was further classified as macrocytic (mean corpuscular volume [MCV] >97 fL), microcytic (MCV<82 fL) and normocytic (intermediate values).

Date and cause of death were determined using data from the electronic medical records. Survival time was calculated in months.

Statistical Analysis
Due to the non-Gaussian distribution of the variables, nonparametric statistical methods were employed. For categorical variables comparisons between independent groups were performed using Pearson's chi-square test or Fisher's exact test. For quantitative variables, we reported medians and interquartile ranges (IQR), and compared groups using the Mann–Whitney *U*-test. Correlations were assessed using Spearman's correlation coefficient (rho). We utilized Kaplan-Meier analysis to generate mortality probability curves for both anemic and non-anemic groups, with group comparisons conducted using the Log rank test. The association between anemia and all-cause mortality was evaluated through Cox proportional hazard regression analysis. Statistical analysis was performed using the "R" software (https://www.r-project.org/).

Results

Patient Characteristics and Mortality

A total of 127 patients were initially included in the study. Two patients were excluded due to lack of follow-up. Finally, data from 125 patients who had been admitted for COPD exacerbation during the study period were analyzed. There were 25 women (20%) and 100 men (80%) with an age (median and IQR) of 73 (67–79) years.

Thirty-one patients (25%) were identified as anemic. Patients with anemia were older, experienced more exacerbations in the previous year, had a lower body mass index, higher comorbidity, and shorter survival. The characteristics of patients based on to the presence or absence of anemia are detailed in Table 1.

By the end of the study, 59 patients (47%) had died, with a median survival of 24 months (IQR: 11–38 months). Among these, 27 out of 31 patients with anemia (87%) and 32 out of 94 patients without anemia (34%) had died. The 66 patients who survived had a minimum follow-up of 38 months and a maximum of 56 months. Hemoglobin levels showed a weak positive correlation with survival in months (r=0.29; p<0.001), as illustrated in Figure 1.

Anemia and Risk of Mortality

Figure 2 displays the mortality probability curves based on the presence of anemia (Kaplan-Meier curves, log-rank analysis of difference with p<0.0001).

Mortality was found to be independent of the type of anemia: macrocytic anemia (MCV >97 fL) was observed in 4 patients, 4 died; microcytic anemia (MCV<82 fL) was observed in 5 patients, of whom 4 died, and normocytic anemia was observed in 22 patients, of whom 19 died.

Factors influencing survival time were analyzed using both univariate and multivariate Cox regression analysis. Mortality rates were notably higher in the group of patients with anemia, both in the short term (one year) and the long term (three years and the end of the study). One year after admission, 10 patients (32%) in the anemia group and 9 (10%) in the group of patients without anemia had died (p=0.002). At this time point, the presence of anemia was associated with a significantly higher mortality rate with a hazard ratio of 4.17 (95%CI: 1.64–10.57, p=0.003) in the univariate analysis, and 5.20 (1.86–14.55, p=0.002) in the multivariate analysis. Notably, in the multivariate analysis, only anemia

Table 1 Characteristics of COPD Patients Based on Anemia

	Patients with Anemia, n=31	Patients Without Anemia, n=94	P value
Age (years)	78 (73–86)	71 (65–78)	<0.001
Gender (F/M), number	3/28	22/72	0.10
Current smokers, n (%)	11 (35%)	34 (36%)	0.70
Pack-year	60 (43–80)	50 (40–64)	0.23
FEV1 (% of predicted)	47 (30–54)	44 (33–51)	0.86
Number of exacerbations	2 (0.5–3)	0 (0–2)	0.01
Dyspnea (mMRC)	3 (2–3)	2 (2–3)	0.09
Body mass index	24 (22–26)	27 (24–30)	<0.01
Charlson (modified)	2 (2–3)	2 (1–3)	<0.01
Length of admission	6 (4–7)	5.5 (4–7)	0.72
Hemoglobin (g/dL)	10.7 (11.8–12.4)	14.6 (13.8–15.6)	<0.001
Survival (months)	26 (11–37)	45 (38–49)	<0.001
Mortality n, (%)	27 (87%)	32 (34%)	<0.001

Note: Values are median (IQR) unless otherwise specified.
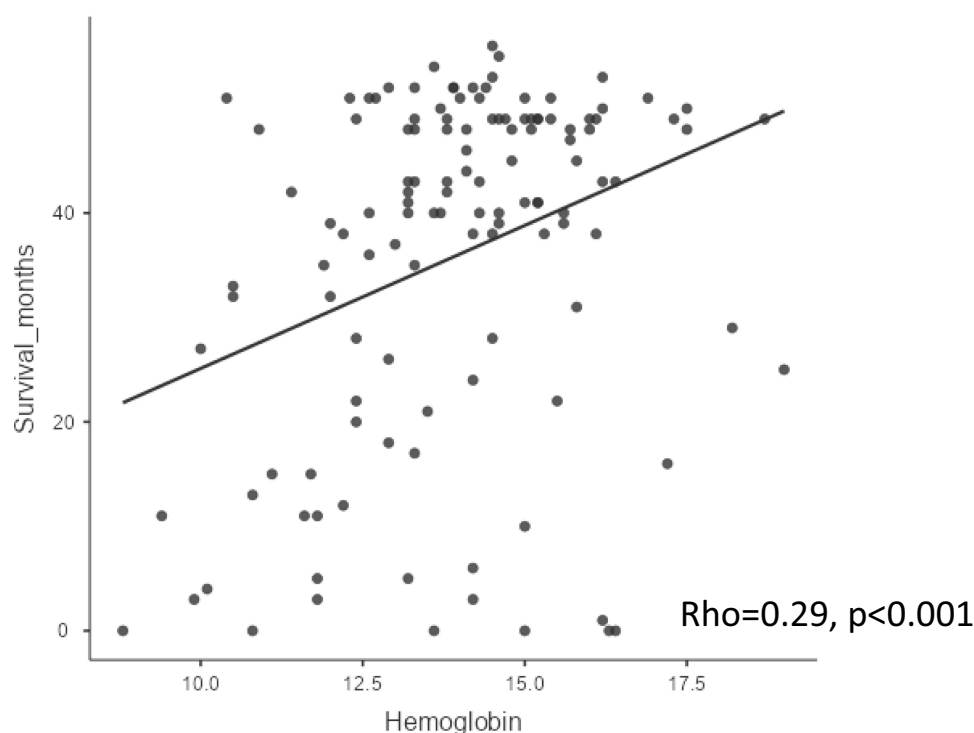**Abbreviations**: F, Female; M, Male; mMRC, Modified Medical Research Council dyspnea scale.

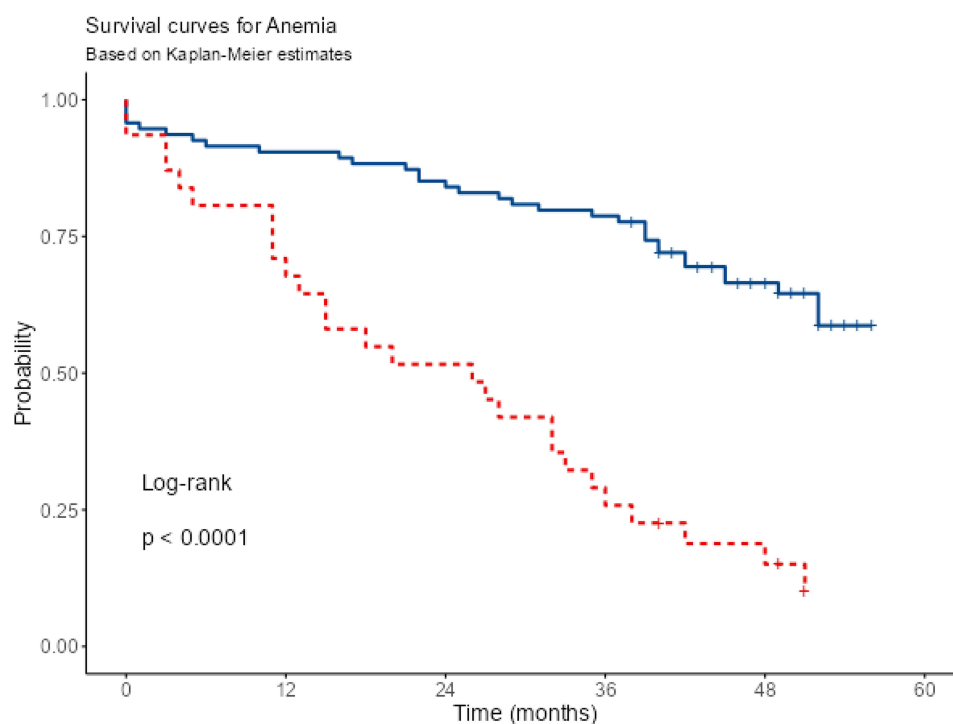**Figure 1** Correlation between hemoglobin level and survival in months.

Figure 2 Survival curves for non-anemic (solid blue line) and anemic (dashed red line).

and dyspnea emerged as independent predictors of mortality at one year. Patient characteristics at one-year categorized by mortality and statistical analysis, are provided in the supplementary material (Table S1 and Table S2).

Three years after admission, 22 patients (71%) in the anemia group and 20 (21%) in the non-anemia group had died (p<0.001). At this time, the hazard ratio for anemia was 4.80 (2.52–9.12, p<0.001) (univariate analysis) and 4.30

(2.03–9.10, p<0.001) (multivariate analysis). Other independent predictors of mortality at 3-year were dyspnea (HR: 2.52 [1.40–4.53, p=0.002]) and the length of hospital admission during exacerbation (HR:1.13 [1.04–1.21, p=0.002]). Patient characteristics at 3-years, categorized by mortality and statistical analysis are detailed in the supplementary material (Table S3 and Table S4).

At the end of the study period, with follow-up until death or a minimum of 38 months and a maximum of 56 months in survivors, mortality in the group of patients with anemia totaled 27 individuals (87%) compared to 32 (34%) in patients without anemia (p<0.001). The characteristics of the deceased patients and survivors are detailed in Table 2. For the multivariate analysis, we included the variables that in the univariate analysis had a p-value of less than 0.05 from the univariate analysis. Anemia emerged as the major independent variable for mortality (HR; 3.80 [1.96–7.38, p<0.001]) (Table 3).

Table 2 Characteristics of COPD Patients Based on Mortality

	Deceased Patients, n=59	Surviving Patients, n=66	P value
Age (years)	77 (72–84)	69 (64–77)	<0.001
Gender (F/M), number	5/54	20/46	0.002
Current smokers, n (%)	19 (32%)	29 (44%)	0.178
Pack-years	60 (50–80)	50 (40–60)	<0.001
FEV1 (% of predicted)	40 (30–51)	46 (36–54)	0.145
Number of exacerbations	2 (0–3)	0 (0–1)	<0.001
Dyspnea (mMRC)	3 (2–3)	2 (1–3)	<0.001
Body mass index	24 (22–28)	28 (24–32)	0.002
Charlson (modified)	2 (1.5–3)	1 (1–3)	0.019
Length of admission	6 (4–8)	5 (3–7)	0.07
Anemia, n (%)	27 (46%)	4 (6%)	<0.001
Hemoglobin (g/dL)	13.0 (11.8–14.6)	14.5 (13.7–15.4)	<0.001
Survival (months)	24 (11–38)	49 (43–51)	<0.001

Note: Values are median (IQR) unless otherwise specified.
Abbreviations: F, Female; M, Male; mMRC, Modified Medical Research Council dyspnea scale.

Table 3 Univariate and Multivariate Hazard Ratios for Mortality

Variable	Univariate HR	Multivariate HR
Anemia	4.56 (2.64–7.86, p<0.001)	3.80 (1.96–7.38, p<0.001)
Gender (male)	3.37 (1.34–8.45, p=0.010)	2.61 (0.99–6.84, p=0.052)
Current smoker	0.65 (0.36–1.16, p=0.143)	
Age	1.05 (1.02–1.08, p=0.001)	1.04 (1.01–1.08, p=0.013)
Dyspnea (mMRC)	1.87 (1.36–2.59, p<0.001)	1.75 (1.17–2.63, p=0.007)
Exacerbations (previous year)	1.26 (1.11–1.43, p<0.001)	1.18 (1.02–1.37, p=0.029)
Pack/years	1.01 (1.01–1.02, p=0.001)	1.00 (0.99–1.01, p=0.51)
Length of admission	1.11 (1.04–1.18, p=0.001)	1.13 (1.05–1.21, p<0.001)

(Continued)

Table 3 (Continued).

Variable	Univariate HR	Multivariate HR
Comorbidity (Charlson modified)	1.22 (0.99–1.51, p=0.062)	
FEV1	0.98 (0.97–1.00, p=0.090)	
Body Mass Index	0.91 (0.87–0.96, p=0.001)	0.97 (0.92–1.03, p=0.35)

Notes: Values are Hazard Ratio with 95% confidence interval.

Table 4 Causes of Mortality

	Patients with Anemia (n=27)	Patients Without Anemia (n=32)	P value
COPD exacerbation	13 (48%)	18 (56%)	0.54
Heart disease	5 (18%)	3 (9%)	0.31
Cancer	4[a] (15%)	7[b] (22%)	0.49
Infection	4 (15%)	3[c] (9%)	0.52

Notes: Number, (%). [a]4 lung cancer, [b]3 lung cancer and 4 digestive cancer. [c]2 COVID-19.

Causes of Mortality

The causes of mortality among patients with or without anemia were similar and are detailed in Table 4. Exacerbation of COPD was the most frequent cause of death.

Discussion

This study shows that the presence of anemia in patients consecutively admitted to the hospital because of COPD exacerbation is a strong predictor of mortality. The increased risk associated with anemia is consistently maintained several years following admission. In our series, the adjusted hazard ratio was 5.20 in the first year, 4.30 at three years, and 3.80 at the end of the study. Throughout all periods, anemia remained the greatest predictor of mortality among the variables analyzed.

Although the association of anemia and mortality is well-known in stable-phase COPD patients, evidence in patients after hospitalization is scarce. Previous studies in hospitalized COPD patients have involved relatively short follow-ups or analyzed samples of patients selected for specific characteristic. Martinez-Rivera et al[11] reported a one-year mortality risk of 5.9 (CI: 1.9–19) associated with anemia in patients admitted with COPD. A register-based cohort study of patients including data only from the first-time admission for acute exacerbation of COPD, demonstrated that the elevated risk of mortality persisted for years after that first hospital discharge.[12] Cireli and Mertoglu[13] followed-up COPD patients hospitalized with respiratory failure and found that anemic patients had lower survival rates after one and two years. In the study by Toft-Petersen et al[12] results showed that anemia was also a predictor of mortality in women hospitalized for COPD exacerbation; however, our series includes a relatively small number of women, and only three had anemia, so no strong conclusions about prognostic differences based on gender can be drawn from our results.

In a large study of non-hospitalized COPD patients, the frequency of anemia was close to 4%, and was more prevalent in patients with uncontrolled disease.[17] In patients hospitalized for COPD exacerbation, the prevalence of anemia is higher, reaching 25% in our series. In other series of hospitalized patients, the prevalence was even greater, up to 38%.[11–13]

Anemia in our patients was most frequently normocytic, although there were some cases of microcytic and macrocytic anemia. A multifactorial mechanism has been implicated in the development of anemia in COPD. The storm of inflammatory mediators during COPD exacerbations may inhibit erythropoiesis.[6,18] Other factors such as poor

renal function, malnutrition, low testosterone levels, abnormalities in growth hormone levels or angiotensin-converting enzyme inhibition may also be associated with the development of anemia.[6] Biomarkers found in anemic individuals suggest inflammation, lung tissue injury, and oxidative stress as possible pathways for the adverse correlations of anemia with outcomes in COPD.[19] Substantial further study is required to better understand these potential mechanisms.[19] There is no evidence to support that treating anemia in these patients modifies prognosis.[20] Not only in patients with COPD, but also in the general hospitalized population, the presence of anemia (mild or moderate and severe) has been independently associated with increased mortality, and transfusion therapy did not improve this risk.[21]

Boutou et al[22] were the first to indicate that anemia (but not the hemoglobin value) is independently associated with survival in stable COPD outpatients. Consequently, it is more adequate to include anemia as a categorial variable[22] as we have done in this study. This is consistent with previous results indicating that low or very high hemoglobin values were associated with increased mortality in COPD patients.[23]

The mortality rate in our study was similar to that reported in an extensive study involving multiple series.[24] A secondary objective of our study was to analyze whether the causes of death in patients with COPD and anemia differed from those without anemia. In COPD patients, the main causes of mortality are respiratory and cardiovascular.[25] It is known that exacerbating COPD patients die more frequently from respiratory causes than non-exacerbating patients.[26] In our series, patients with anemia did not appear to have a differentiate underlying disease that led to their death. The cause of mortality was similar in both groups of patients, with respiratory causes predominating.

While anemia is recognized as a prognostic factor in COPD patients, this clinical characteristic has not been incorporated into the multidimensional indices for prognostic prediction that have been proposed.[3] In light of our results and those of previous studies, it seems reasonable to propose that anemia should be included in multifunctional indices for predicting mortality in COPD.

This study has some limitations. Firstly, it was performed in a single center, and patient characteristics or admission criteria may differ in other centers. Additionally, the number of patients included may be relatively small due to the study's duration overlapping with the COVID-19 pandemic, resulting in fewer admissions for other pathologies.[27] However, it does not appear that this pandemic significantly influenced the mortality of our patients, as only two of them died from COVID-19. Despite these limitations, the study has strengths in its design that bolster the value of its results. It is a real-world study of consecutive patients, followed for a lengthy period with virtually no patient losses, and the results are consistent with and support those of previous studies with similar populations.

Conclusion

Exacerbation in COPD patients is associated with an increased risk of mortality. Despite efforts to identify factors linked to this risk and to propose multifactorial indices for prediction, anemia, a well-known risk factor for mortality, has not been considered in this patient population.

However, anemia, which is a known risk factor for mortality, has not been taken into account for this purpose in this target group of patients.

Anemia serves as a prognostic factor in various circumstances among COPD patients. Based on our experience with hospitalized COPD patients, we have observed that anemia detected upon admission for COPD exacerbation correlates with a substantial rise in the risk of death in the ensuing years. Anemia emerges as perhaps the most potent predictor of death in these patients. Given that anemia can be readily, inexpensively, and routinely detected during admission, our findings advocate for its utilization as a mortality predictor and propose its integration into any proposed indices for this purpose.

Data Sharing Statement

The data that support the findings of this study are available upon justified request to the corresponding author.

Ethics Approval and Informed Consent

The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Clinical Research Ethics Committee of the Elche Health Department-Hospital General (Ref. PI 31/2019). Written informed consent was obtained from all participants before their inclusion in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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