

Impact of anemia on short-term survival in severe COPD exacerbations: a cohort study

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Purpose: Anemia is reported to be an independent predictor of hospitalizations and survival in COPD. However, little is known of its impact on short-term survival during severe COPD exacerbations. The primary objective of this study was to determine whether the presence of anemia increases the risk of death in acute respiratory failure due to severe COPD exacerbations.

Patients and methods: Consecutive patients with COPD exacerbation who were admitted to the intensive care unit with the diagnosis of acute respiratory failure and required either invasive or noninvasive ventilation (NIV) were analyzed.

Results: A total of 106 patients (78.3% male; median age 71 years) were included in the study; of them 22 (20.8%) needed invasive ventilation immediately and 84 (79.2%) were treated with NIV. NIV failure was observed in 38 patients. Anemia was present in 50% of patients, and 39 patients (36.8%) died during hospital stay. When compared to nonanemic patients, hospital mortality was significantly higher in the anemic group (20.8% vs 52.8%, respectively; $P=0.001$). Stepwise multivariate logistic regression analysis showed that presence of anemia and NIV failure were independent predictors of hospital mortality with odds ratios (95% confidence interval) of 3.99 ([1.39–11.40]; $P=0.010$) and 2.56 ([1.60–4.09]; $P<0.001$), respectively. Anemia was not associated with long-term survival in this cohort.

Conclusion: Anemia may be a risk factor for hospital death in severe COPD exacerbations requiring mechanical ventilatory support.

Keywords: chronic obstructive pulmonary disease, exacerbation, acute respiratory failure, mortality, anemia, noninvasive ventilation

Introduction

COPD is a major cause of health burden throughout the world.¹ COPD often coexists with comorbidities such as cardiovascular diseases, osteoporosis, skeletal muscle dysfunction, depression, and anemia.^{2,3} The common ground for most of these extrapulmonary problems is the ongoing severe inflammation. Comorbidities have an influence on potentiating the overall morbidity of COPD, leading to increased hospitalizations, health care costs, and eventually death.

Anemia is a well-known comorbidity of COPD with a prevalence ranging from 12.3 to 23%.^{3–5} Previous studies also showed that the prevalence is much higher during exacerbations.^{6–8} Anemia in COPD is directly associated with adverse clinical outcomes, including death. Hemoglobin levels correlated with dyspnea scores, exercise capacity, and several inflammatory markers in COPD.^{9–12} Anemia has also been shown as an independent predictor of recurrent hospitalizations and survival in COPD patients with chronic respiratory failure.^{13,14}

It has been suggested that low hemoglobin levels may impair gas exchange and cardiorespiratory interaction in COPD patients.^{4,11} This effect is expected to be more prominent in severe COPD exacerbations presenting with acute respiratory failure

in which the oxygen demand is supposed to be high due to increased respiratory workload. In this study, we sought to identify whether anemia is related with higher in-hospital deaths in severe COPD exacerbations. Secondary end points were to evaluate the impact of anemia on noninvasive ventilation (NIV) failure and long-term survival.

Patients and methods

Study population

This cohort study was conducted in a 14-bed medical intensive care unit (ICU) of a tertiary reference hospital. The ethics committee of Dışkapı Yıldırım Beyazıt Education and Research Hospital approved the study (approval number: 10/29). Written informed consent was obtained to be included in this study from either the patient him/herself or patient's relatives. All consecutive COPD exacerbation patients who developed acute respiratory failure were evaluated between April 2012 and September 2015. Diagnosis of COPD was confirmed, according to the Global initiative for chronic Obstructive Lung Disease (GOLD), from medical records, and if available pulmonary function tests (PFTs) within the previous year.¹ In patients for whom PFTs were unavailable, COPD diagnosis was confirmed with GOLD clinical criteria (age >40 years, >10 pack-year smoking or biomass history).

The exclusion criteria were as follows: 1) suspected alternative/additional cause for respiratory failure such as pneumonia, pulmonary embolism, cardiogenic pulmonary edema, severe sepsis, acute respiratory distress syndrome, 2) presence of active bleeding, 3) presence of a disease/treatment possibly associated with bone marrow suppression (renal failure with glomerular filtration rate <30 mL/min/1.73 m², malignancy, hematologic disorders), and 4) recent operation or transfusion history.

Demographic characteristics (age, sex, smoking history), recent PFTs – if available, presence of comorbidities, use of long-term oxygen therapy and domiciliary NIV, duration of hospital stay prior to ICU admission, severity scores of Acute Physiology and Chronic Health Evaluation (APACHE) II and Glasgow Coma Scale (GCS) were recorded.

Laboratory data for admission arterial blood gas analysis, complete blood cell count, and serum CRP were collected. Anemia was defined as hemoglobin levels <12 gm/dL for female patients and <13 gm/dL for male patients according to the World Health Organization (WHO) anemia definition.¹⁵

Data collection for mechanical ventilation and follow-up

All patients had acute respiratory failure due to an exacerbation and were supported by either invasive (mechanical

ventilation with endotracheal intubation) ventilation or NIV according to the degree of respiratory failure and the patient's clinical condition. NIV was performed by experienced ICU staff using pressure support mode through an oronasal mask. NIV failure was defined as requiring endotracheal intubation at any time.

Initial mechanical ventilation support type, failure in NIV, total duration of mechanical ventilation support, the lengths of ICU and hospital stays, and ICU and hospital mortality were recorded. For survivors, mortality was evaluated from the national death database system on January 31, 2016.

Statistical analysis

The primary outcome of the study was whether the presence of anemia on admission is a risk factor for hospital mortality in severe COPD exacerbations. Secondary outcomes were the effect of anemia on NIV failure and long-term survival. The sample size (n=106) was calculated assuming an alpha error of 5% to reject the null hypothesis with a statistical power of 80% and anticipating 5% dropout rate.¹⁶

All categorical variables are expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range. Categorical variables between groups were compared with chi-square or Fisher's exact test, continuous variables were compared with Mann–Whitney *U*-test. The independent effect of anemia on hospital mortality was assessed with stepwise multivariate logistic regression analysis. To build the model, a purposeful selection method was used to select a subset of covariates that were considered to be clinically important, adjusting for confounders and statistical significance. An adjusted odds ratio (OR) and a 95% confidence interval (CI) were reported for each independent factor. A two-tailed *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences Version 20; IBM Corporation, Armonk, NY, USA) program.

Results

Study flowchart is presented in Figure 1. A total of 124 patients were screened and 106 patients (78.3% male; median age 71 years) were included in the study. Patient characteristics are shown in Table 1. PFTs were available in 62 patients; the median (interquartile range) forced expiratory volume in 1 second (FEV₁) % predicted was 31.4% (20.5%–40.2%). Thirty-seven (34.9%) patients were using long-term oxygen therapy and 15 (14.2%) patients were using NIV at home. Hypertension and coronary artery disease were the most common comorbidities. Twelve patients had a respiratory arrest event before ICU admission. On ICU admission, the

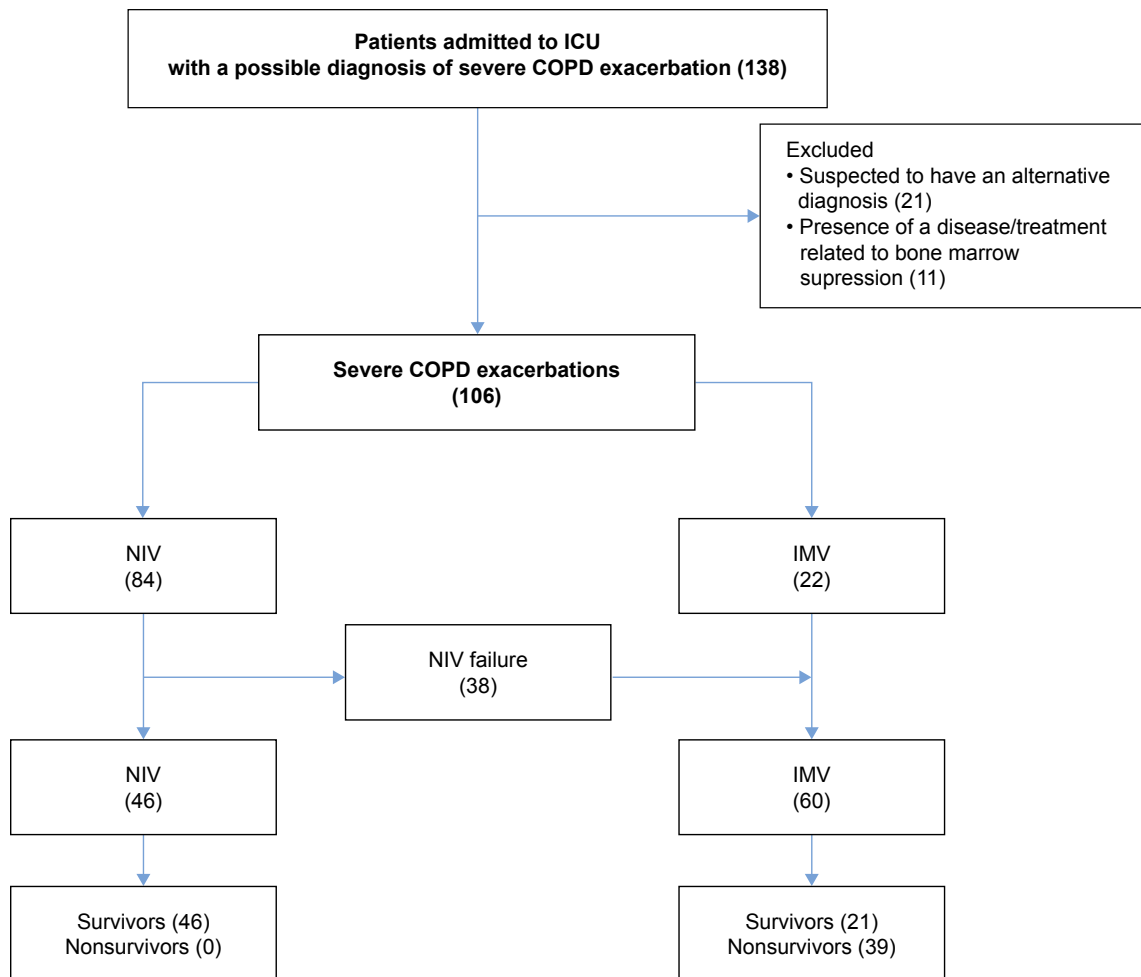


Figure 1 Study flowchart and hospital outcomes of the study population.

Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation.

median APACHE II and GCS scores were 23.0 (18.0–31.0) and 15.0 (8.0–15.0), respectively.

Mechanical ventilation support and NIV failure

Admission arterial blood gas analysis showed patients had hypercapnic respiratory failure. The median pH and arterial partial pressure of CO₂ were 7.26 (7.18–7.31) and 75.8 (62.7–85.1) mmHg, respectively (Table 2). Twenty-two patients had invasive mechanical ventilation at the time of ICU admission, whereas 84 patients were first treated with NIV. During follow-up, NIV failure was observed in 38 patients with a median duration of 2.5 (0.3–10.0) days. The statistically significant factors between NIV successful and failed patients are shown in Table 3. There was no difference for mechanical ventilation duration between both groups ($P=0.917$). Hospital mortality was 65.8% in the NIV failed group whereas there were no deaths in the NIV successful group.

Hemoglobin levels and presence of anemia

The median hemoglobin level was 12.8 (11.6–15.0) gm/dL in the whole study population. Only one patient had polycythemia (hemoglobin >18.5 gm/dL). Hemoglobin levels were negatively correlated with age ($r=-0.293$, $P=0.002$) and positively correlated with FEV₁ % predicted ($r=0.388$, $P=0.011$) (Figure 2A and B). Anemia was present in half of the patients ($n=53$) and there was no difference between sex groups (49.4% [41/83] of male and 52.2% [12/23] of female patients were anemic; $P=1.00$). The median hemoglobin level in the anemic group was 11.6 (10.2–12.3) gm/dL whereas it was 15.0 (13.7–16.1) gm/dL in the nonanemic group (Figure 3). Mean corpuscular volume did not differ between anemic and nonanemic patients (86.4 [79.9–91.4] and 88.7 [84.6–91.8] fL, respectively, $P=0.245$). Anemic patients were older, had lower FEV₁ % predicted, and had higher APACHE II score (Table 4). NIV failure was observed more in the anemic

Table 1 General characteristics of study population

N	106
Sex	
Male	83 (78.3)
Female	23 (21.7)
Age, years	71.0 (62.0–76.0)
Previous smoking history/active smoking	59 (55.7)/25 (23.6)
Pack-years	60.0 (60.0–96.3)
Pulmonary function tests ^a	
FEV ₁ (liters)	0.79 (0.59–1.17)
FEV ₁ % predicted	31.4 (20.5–40.2)
Long-term oxygen therapy	37 (34.9)
Domiciliary NIV	15 (14.2)
Comorbidities	
• Hypertension	60 (56.6)
• Coronary artery disease	35 (33.0)
• Diabetes mellitus	30 (28.3)
• Arrhythmia	22 (20.8)
• Congestive heart failure	21 (19.8)
GCS score	15.0 (8.0–15.0)
APACHE II score	23.0 (18.0–31.0)
Respiratory arrest before ICU admission	12 (11.3)
Length of stay (days) between hospital admission and ICU admission	1.0 (0.0–5.0)

Notes: All values are expressed as numbers (percentages) or median (interquartile range). ^aPulmonary function tests were available in 62 patients.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FEV₁, forced expiratory volume in 1 second; GCS, Glasgow Coma Scale; ICU, intensive care unit; NIV, noninvasive ventilation.

Table 2 Clinical characteristics of study population

Mechanical ventilation support	
Invasive ventilation	22 (20.8)
NIV	84 (79.2)
NIV failure	38 (35.8)
Duration of mechanical ventilation (days)	7.0 (3.0–18.0)
Admission arterial blood gas values	
pH	7.26 (7.18–7.31)
PaCO ₂ (mmHg)	75.8 (62.7–85.1)
PaO ₂ (mmHg)	52.0 (40.4–64.5)
PaO ₂ /FiO ₂	130.0 (101.0–161.3)
Lactate (mmol/L)	1.6 (1.1–2.5)
White blood cell count (×10 ³ /μL)	12.2 (8.7–17.3)
CRP (mg/L)	8.9 (3.5–13.5)
Hemoglobin (gm/dL)	12.8 (11.6–15.0)
Hematocrit (%)	40.8 (35.9–48.7)
MCV (fl)	88.3 (82.4–91.7)
Anemia	53 (50)
Polycythemia	1 (0.9)
ALB (gm/dL)	3.3 (2.9–3.6)
ICU length of stay (days)	13.0 (7.8–21.0)
Hospital length of stay (days)	20.0 (12.8–32.0)
ICU mortality	37 (34.9)
Hospital mortality	39 (36.8)

Note: All values are expressed as numbers (percentages) or median (interquartile range).

Abbreviations: ICU, intensive care unit; MCV, mean corpuscular volume; NIV, noninvasive ventilation; CRP, C-reactive protein; ALB, albumin.

Table 3 Statistically significant differences between noninvasive ventilation successful and failed patients (n=84)

Variables	NIV successful (n=46)	NIV failed (n=38)	P-value
APACHE II score	18.0 (15.8–22.0)	27.5 (20.0–32.8)	<0.001
GCS score	15.0 (15.0–15.0)	12.0 (5.5–15.0)	<0.001
Arrhythmia	7 (10.4)	15 (38.5)	0.041
Domiciliary NIV use	11 (23.9)	4 (10.5)	0.047
CRP (mg/L)	6.3 (1.8–13.3)	10.8 (6–16.4)	0.036
Hemoglobin (gm/dL)	14.0 (12.5–15.5)	11.9 (10.9–13.3)	<0.001
Hematocrit (%)	45.2 (38.9–51.2)	37.6 (34.6–42.2)	0.001
Anemia	14 (30.4)	26 (68.4)	0.001
Hospital length of stay (days)	15.0 (9.5–22.0)	23.5 (18.0–38.0)	0.001
Hospital mortality	0 (0.0)	25 (65.8)	<0.001

Note: All values are expressed as numbers (percentages) or median (interquartile range).

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; NIV, noninvasive ventilation; CRP, C-reactive protein.

patients when compared to the nonanemic group (49% vs 22.6%, respectively; $P=0.001$).

Short-term mortality

Thirty-nine patients (36.8%) died during hospital stay (Table 5). When compared, nonsurvivors had higher APACHE II and lower GCS scores, had more domiciliary NIV use, and low serum ALB. Hospital mortality was 52.8% in the anemic group, whereas it was 20.8% in the nonanemic group ($P=0.001$). Logistic regression analysis for hospital mortality (Table 6), showed presence of anemia and NIV failure were independent predictors of hospital death with ORs (95% CI) of 3.99 ([1.39–11.40]; $P=0.010$) and 2.56 ([1.60–4.09]; $P<0.001$), respectively. When hemoglobin levels (continuous variable) were used instead of anemia (categorical variable) in the regression model, OR for hospital mortality was 0.74 (0.59–0.94; $P=0.014$).

Long-term mortality

Sixty-seven patients were discharged from hospital. Median follow-up time was 314 (47–773) days. During this period, 26 patients died. Overall mortality was 38.7% (n=41) for 28 days, 50.9% (n=54) for 3 months, and 61.3% (n=65) for 1 year. Hemoglobin levels did not differ between survivors and nonsurvivors ($P=0.903$).

Discussion

Anemia of chronic disease is relatively common and an important factor in the natural history of COPD. In this study, the presence of anemia was associated with increased

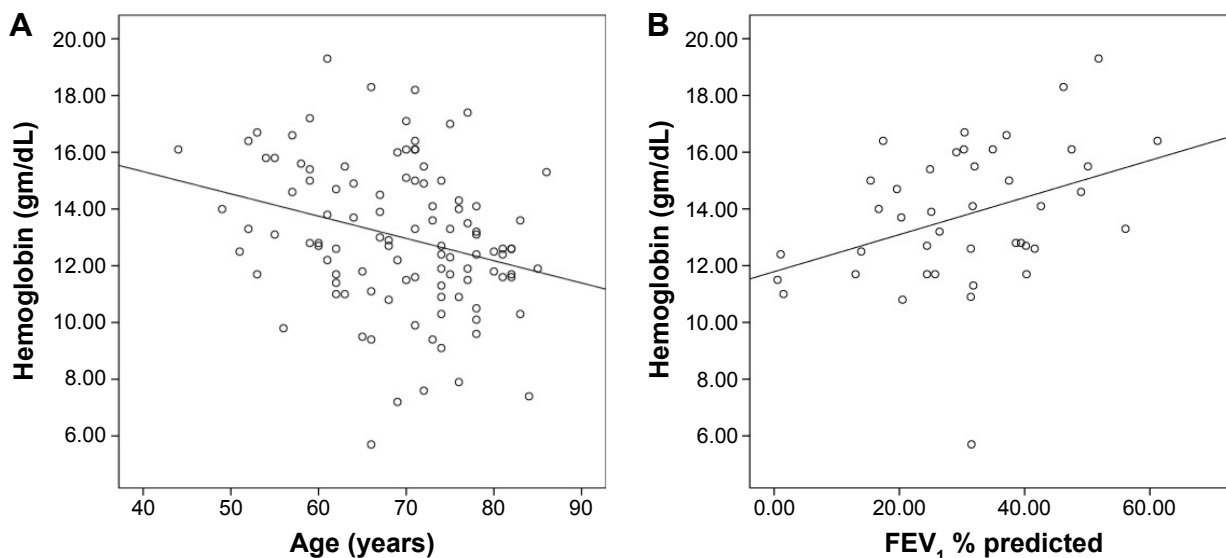


Figure 2 Correlations between hemoglobin concentration and age and FEV₁% predicted.
Notes: (A) The correlation between hemoglobin and age (Spearman's correlation coefficient: -0.293 ; $P=0.002$). (B) The correlation between hemoglobin and FEV₁ % predicted ($n=62$; Spearman's correlation coefficient: 0.388 ; $P=0.011$).
Abbreviation: FEV₁, forced expiratory volume in 1 second.

hospital mortality in severe COPD exacerbations requiring mechanical ventilation support.

Anemia as a comorbidity in COPD

Anemia is a comorbidity of severe COPD and responsible for increased disease burden.³⁻⁶ Anemic patients experience more dyspnea and have decreased functional capacity which in turn results in deterioration in the quality of life.⁹⁻¹¹ Additionally these patients exacerbate more and have higher risk of death than nonanemic patients.^{6,17,18} It is also reported to be an independent negative predictor of the duration of

hospitalizations and survival of COPD patients receiving oxygen therapy.¹⁴

The prevalence of anemia is approximately 33%–44% in patients hospitalized for an exacerbation.^{7,8,19} In the present study, anemia was detected in 50% of patients with exacerbations. This result is relatively higher than previously reported, possibly because the study population comprised patients with more severe COPD. We have also found that hemoglobin levels were correlated with FEV₁ % predicted and anemic patients had lower FEV₁ than nonanemic patients which is consistent with previously reported data.^{10,14}

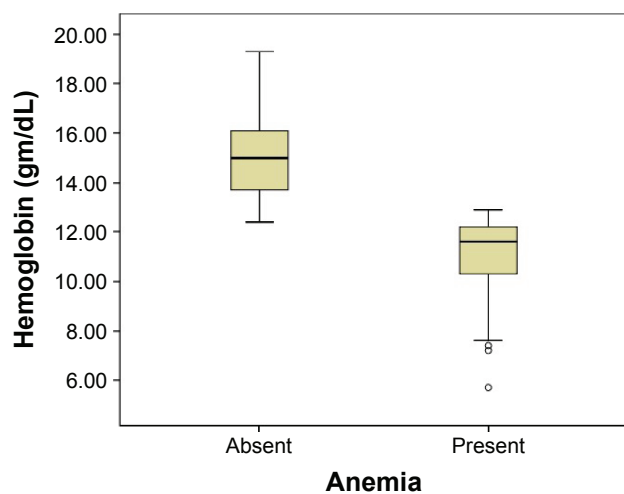


Figure 3 Hemoglobin levels in anemic and nonanemic patients.

Table 4 Statistically significant differences between anemic and nonanemic patients

Variables	Anemic patients (n=53)	Nonanemic patients (n=53)	P-value
Age (years)	74.0 (65.0–78.0)	70 (59.0–74.0)	0.018
FEV ₁ % predicted ^a	25.7 (13.5–35.2)	32.0 (25.0–46.9)	0.042
APACHE II score	26.0 (19.0–31.5)	21.0 (17.0–29.0)	0.016
Coronary artery disease	23 (43.4)	12 (22.6)	0.038
Arrhythmia	17 (32.1)	5 (9.4)	0.007
Hemoglobin (gm/dL)	11.6 (10.2–12.3)	15.0 (13.7–16.1)	<0.001
NIV failure	26 (49.0)	12 (22.6)	0.001
Hospital length of stay (days)	26.0 (13.5–40.0)	18.0 (11.5–24.5)	0.048
Hospital mortality	28 (52.8)	11 (20.8)	0.001

Notes: All values are expressed as numbers (percentages) or median (interquartile range). ^aAvailable in 62 patients.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FEV₁, forced expiratory volume in 1 second; NIV, noninvasive ventilation.

Table 5 Statistically significant factors related with hospital mortality

Variables	Survivors (n=67)	Nonsurvivors (n=39)	P-value
APACHE II score	20.0 (17.0–28.0)	28.0 (22.0–34.0)	<0.001
GCS score	15.0 (12.0–15.0)	10.0 (5.0–10.0)	<0.001
Arrhythmia	7 (10.4)	15 (38.5)	0.001
Domiciliary NIV use	13 (19.4)	2 (5.1)	0.047
NIV failure	13 (19.4)	25 (64.1)	<0.001
CRP (mg/L)	6.9 (1.9–12.5)	11.0 (5.9–17.3)	0.009
Hemoglobin (gm/dL)	13.6 (12.4–15.5)	11.6 (10.3–13.3)	<0.001
Hematocrit (%)	42.6 (38.7–50.5)	36.5 (32.2–43.7)	<0.001
Anemia	25 (37.3)	28 (71.8)	0.001
ALB (gm/dL)	3.4 (3.0–3.7)	3.0 (2.7–3.3)	0.003
Hospital length of stay (days)	17 (12–25)	26 (16–39)	0.030

Note: All values are expressed as numbers (percentages) or median (interquartile range).

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; NIV, noninvasive ventilation; CRP, C-reactive protein; ALB, albumin.

Anemia and short-term prognosis in severe COPD exacerbations

Although the impact of anemia during stable phase of COPD was reported in many longitudinal cohort studies, the effect of anemia on clinical outcomes for COPD exacerbations, particularly in the ICU setting, was studied less.^{20–23} In this study, the presence of anemia is associated with an increased risk of death in severe COPD exacerbations with an OR of 3.99. We propose anemia should be considered as a risk stratification factor for severe COPD exacerbations in the ICU.

Anemia has been shown to be associated with increased mortality in COPD-related acute respiratory failure.^{8,20–23} Rasmussen et al²² evaluated COPD patients who needed invasive ventilation and found that 54.8% of anemic COPD patients died within 30 days with a mortality risk ratio of 3.1 (95% CI 1.6–5.9). Another study reported that hemoglobin level was an independent predictor of hospital mortality

Table 6 Stepwise multivariate logistic regression analysis for independent predictors of hospital mortality

Variable	Odds ratio	95% confidence interval	P-value
Age	1.00	0.93–1.06	0.874
APACHE II score	0.97	0.90–1.05	0.470
GCS score	0.90	0.78–1.03	0.123
Arrhythmia	2.80	0.89–8.87	0.080
Domiciliary NIV	0.32	0.07–2.38	0.323
ALB	0.47	0.18–1.29	0.146
NIV failure	2.56	1.60–4.09	<0.001
Anemia	3.99	1.39–11.40	0.010

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; NIV, noninvasive ventilation; ALB, albumin.

(OR: 0.63, 95% CI: 0.45–0.90; $P=0.006$).²³ The impact of anemia on COPD exacerbations was also evaluated in the emergency room setting; a multicenter study performed in Canada showed anemia (hemoglobin <10 gm/dL) was the strongest predictor (OR 4.9; 95% CI 2.1–11.7) of serious adverse events including death in patients admitted to the emergency room.²⁴ All these data suggest that, besides being an important predictor of long-term survival, anemia should also be considered as a risk factor for short-term mortality in severe COPD exacerbations.

The mechanisms of the development of anemia in COPD are complex and outside the scope of this article, nevertheless disease severity seems to be one of the most important factors.²⁵ Anemia was proposed as a marker for end-stage COPD.²² COPD is a systemic inflammatory disease in which many cytokines, including IL-1, IL-6, and TNF-alpha, play a role. These cytokines are also involved in inhibition of erythropoiesis at different steps of the erythropoietic pathway. In the presence of severe systemic inflammation, impairment of erythropoiesis becomes evident as anemia of chronic inflammation.^{5,25} In addition to chronic changes in the erythropoiesis, acute changes in hemoglobin levels were also reported during exacerbations. Markoulaki et al²⁶ showed that a severe exacerbation itself caused transient changes in hemoglobin levels with a median decrease of 1.3 gm/dL. There was a negative correlation between hemoglobin and erythropoietin (EPO) levels which points out increased EPO resistance during exacerbations. It is already known that EPO resistance is directly correlated with the levels of inflammatory cytokines and therefore the level of systemic inflammation. Repeated exacerbations could further inhibit erythropoiesis, and as a result a significant decrease in hemoglobin levels can occur in severe COPD. Thus, anemia could be accepted as a surrogate of severe systemic inflammation and might be helpful in identifying sicker patients.

Additionally, another important mechanism responsible for the development of anemia of chronic disease is the alteration in iron metabolism.^{5,7,27} Increased levels of inflammatory cytokines and hepcidin, a peptide hormone that regulates iron homeostasis, also play a significant role in impaired iron utilization which causes functional iron deficiency. It has been shown that functional iron deficiency, even before the onset of anemia, is related to hypoxemia, more frequent self-reported exacerbations, decreased exercise tolerance, and limited response to pulmonary rehabilitation.^{27,28} Recently, it was suggested that specific attention should be paid to iron deficiency even in the absence of anemia, and iron supplementation may be helpful in anemic COPD patients.²⁹

Researches performed in other chronic inflammatory diseases and one study done in COPD with renal impairment have shown improvement in patient outcomes with iron replacement.^{7,30} However, more data are needed to understand the importance of functional iron deficiency in COPD and the beneficial effect of iron replacement needs to be confirmed with randomized controlled trials.

On the other hand, COPD patients might be more sensitive to anemia than we think. This hypothesis is supported by the data from two previous studies. COPD patients were reported to have higher a mortality rate during gastrointestinal bleeding when compared to non-COPD patients.³¹ In the second study, low hematocrit levels were associated with worse outcomes in COPD patients after elective open abdominal aortic aneurysmectomy.³² The reason for this negative effect of anemia on outcomes is still unknown. However, from the physiological point of view, anemia causes a decrease in oxygen transport capacity of blood which could impair physiological and clinical parameters in COPD.⁴ Yuruk et al showed that low hemoglobin levels were associated with impaired tissue oxygen saturation in the microcirculation, and hemoglobin correction resulted in improvement in oxygen carrying capacity and tissue oxygen saturation.^{33,34} The negative effect of low hemoglobin levels on tissue oxygenation might be clinically important in severe COPD, especially during exacerbations.

The current study also showed NIV failure is more common in anemic COPD patients. Haja Mydin et al⁸ looked for prognostic factors in hypercapnic respiratory failure and showed that anemia was related to increased risk of NIV failure. A COPD database study (n=132,424) showed anemic patients had not only more ICU admissions but also needed more ventilatory support.³⁵ Anemia was also reported as a risk factor for extubation and weaning failure.^{36,37} Depending on its severity, anemia is associated with increased work of breathing and reduced exercise tolerance in COPD.^{4,9,11} It has been shown that the relationship between muscle oxygenation and peak oxygen consumption varies widely in COPD, and oxygen consumption is highly influenced by blood oxygenation and oxygen utilization level.^{4,38} Anemic COPD patients also exhibit decreased diffusing capacity corrected for hemoglobin.¹⁹ All these changes in oxygen transport lead to decrease in aerobic capacity and therefore skeletal muscle dysfunction in severe COPD during exercise. One can expect these changes to be more evident in patients with low hemoglobin levels, especially during exacerbations because of increased oxygen demand due to increased work of breathing and impaired cardiopulmonary

interactions. A case series study done by Schönhofer et al³⁹ showed transfusion decreases minute ventilation and work of breathing in anemic COPD patients. The same group also showed that transfusion helped successful weaning from ventilator in five patients.⁴⁰ However, the relationship between anemia and ventilation is complex and more data are needed to understand the consequences of anemia on gas exchange and transport during “pump failure” in COPD.

The optimum threshold for hemoglobin in COPD patients is still being debated. Usually a hemoglobin level of >10 gm/dL is considered as a “safe” zone, however this may not be true for COPD patients. The ANTADIR study showed every 5% increase in hematocrit level was associated a relative risk of 0.86 (0.83–0.89) for 3-year mortality.¹⁴ Kollert et al¹³ proposed hemoglobin values greater than 14.3 gm/dL for females and 15.1 gm/dL for males, which are much higher than WHO’s definition, were associated with better outcomes in patients with chronic respiratory failure. Although hemoglobin levels between 7–9 gm/dL are considered as tolerated well in the ICU setting, Rasmussen et al²² reported a cutoff value of hemoglobin level <12 gm/dL was related to increased risk of death in intubated COPD patients. Interestingly, Stiell et al²⁴ showed that patients with exacerbations who ended up with a serious adverse event (including ICU admission, need for mechanical ventilation, and death within 30 days) had hemoglobin levels of 12.3 gm/dL which could be considered as normal. In regard to these findings, the “safe” hemoglobin level for COPD is probably higher than our standard anemia definitions.

Anemia and long-term prognosis in severe COPD exacerbations

Studies done in COPD with chronic respiratory failure have shown the presence of anemia was associated with worse long-term survival, however, we were not able to show such an effect in our cohort.^{13,14,18} It should be kept in mind that the current study was designed and powered for the primary outcome (hospital mortality). Another important point to consider is study subjects had acute respiratory failure and only one third of the patients had chronic respiratory failure and were using oxygen at home. Finally, the follow-up period might have been too short to see a difference. When compared to previous reports, our median follow-up time was relatively shorter (36 vs 10.5 months, respectively).¹³

Limitations and strengths of the study

This study has several important limitations. First, it is a single-center study and the results may not be generalizable

to other centers. Second, all patients did not have recent PFTs; therefore, we were unable to assess disease severity according to the GOLD classification system in the whole cohort. Third, mortality in the critically ill patients may potentially have been influenced by many confounding factors. Although we have attempted to include a wide range of all possible confounders in the mortality analysis, there is still a lack of data on therapy and complications during ICU stay. Another important point to consider is the etiology of anemia, including data for previous exacerbations and hospitalizations, was not evaluated in this study.

Besides these limitations, the present study has some important strengths. There is limited data about the impact of anemia on severe COPD exacerbations requiring mechanical ventilatory support. Most of the studies done in the ICU setting included not only patients with exacerbations but also patients with other diagnoses such as pneumonia and cardiogenic pulmonary edema.^{20–23} We were meticulous to include only patients with exacerbations. Moreover, the study cohort consisted of patients with different degrees of acute respiratory failure treated with both NIV and invasive ventilation; therefore, our results might apply to a greater percentage of patients for prediction of prognosis. Finally, comorbidities such as congestive heart failure are known to have an increased risk of death in the presence of anemia. For this reason, instead of using a comorbidity index, each comorbidity was assessed separately in order to understand its own relationship with anemia and mortality.

Conclusion

This study highlights two important results: first, anemia is related with increased risk of death in acute respiratory failure due to severe COPD exacerbations. Second, anemia is associated with NIV failure. Further studies are needed to understand the physiological consequences of anemia in COPD exacerbations and its impact on clinical outcomes. Whether correction of anemia has beneficial effects in COPD is another challenging research question waiting to be answered.

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Disclosure

The authors report no conflicts of interest in this work.

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