The impact of anemia on the mortality of COPD patients hospitalized for acute exacerbation resulting in respiratory failure

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Abstract

Anemia increases mortality in patients with chronic obstructive pulmonary disease (COPD), but its effects on mortality and survival time for different levels of airflow limitation severity are unclear. Our goal was to investigate the effects of anemia on survival time and mortality in COPD patients with varying degrees of airflow limitation. We looked at 300 consecutive COPD patients in the past. Their demographic information, Charlson comorbidity index, previous early (30 days) and late (>30 days) hospitalizations, blood counts, and post-bronchodilator spirometric values were all recorded. They were contacted by phone to check on their vital status, and their mortality rates were calculated. Anemic patients had a mean overall survival time of 31.9±2.8 months and normal patients had a mean overall survival time of 41.7±2.2 months (p=0.001). Their 1-year and 2-year mortality rates are higher. Age, Charlson comorbidity index, BMI, FEV_1%, anemia, MCV, hemoglobin, serum creatinin, and early and late hospitalizations all had an impact on mortality. BMI, anemia, and FEV_1% remained risk factors for death. Anemic group 2 patients had a higher mortality rate than groups 3 and 4. Anemic patients in groups 2 and 4 had shorter survival times. Anemic COPD patients have higher 1-year and 2-year mortality rates. Mortality is affected by age, Charlson comorbidity index, BMI, FEV_1%, anemia, MCV, hemoglobin, serum creatinin, and early and late hospitalizations. BMI, anemia, and FEV_1% remained as risk factors factors for death. Anemic group 2 patients have a higher mortality rate than groups 3 and 4. Anemic patients in groups 2 and 4 have shorter survival times.

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Introduction

COPD is caused by a number of factors that activate both the acute and chronic immune systems. Anemia affects 7.5-33% of COPD patients [1]. Anemia is one of the associated diseases that increases COPD patients' mortality and morbidity [2,3]. It increases mortality in patients with stable COPD and those on oxygen therapy [4-8]. Although many studies show that anemia increases mortality in COPD, there is limited data [9,10] on whether it increases mortality as FEV_1% decreases. Our study sought to investigate the effects of anemia on the survival time and mortality of COPD patients with varying FEV_1% values.

Materials and Methods

Study population

We analyzed the patients hospitalized with COPD acute exacerbation (with ICD code J 44.0 and J 44.1) in January 2016-January 2017 interval. The study was a retrospective cross-sectional study conducted in Health Sciences University Dr Suat Seren Chest Diseases and Chest Surgery Training and Research

Hospital, which was a tertiary chest diseases hospital in Izmir, Turkey.

Inclusion criteria

We included patients who were hospitalized in one pneumology department ward for COPD acute exacerbation. COPD patients in respiratory failure are internalized in our institution; therefore, all our patients were in respiratory failure and used oxygen during hospitalization. We analyzed the records of 300 consecutive patients. We diagnosed COPD by using clinical and radiological features and previous spirometries, if available. They were usually in treatment for COPD before hospitalization. The presence of COPD exacerbation was determined at their discharge and post-bronchodilator spirometers were performed one month after they were discharged and were stable. Severity groups were defined according to GOLD 2022 airflow limitation severity criteria, which were based on post-bronchodilator FEV_1%. Airflow limitation severity criteria [2] are: In patients with FEV_1/ FVC <0.70: Group 1: (Mild) $FEV_1 \geq 80\%$ predicted. Group 2: (Moderate) $50\% \leq FEV_1 < 80\%$ predicted. Group 3: (Severe) $30\% \leq FEV_1 < 50\%$ predicted. Group 4: (Very severe) $FEV_1 < 30\%$ predicted.

Demographic data, BMI (kg/m^2), associating diseases (Charlson comorbidity index), previous early (30 days) and late (> 30 days) hospitalizations, ICU (intensive care unit) admission, chronic long term oxygen therapy (LTOT) and non-invasive mechanical ventilator (NIMV) use at home, complete blood counts drawn at emergency room admission, serum C-reactive protein (CRP) and serum creatinine, post-bronchodilator spirometers and arterial blood gas values were recorded on a standardized database. Previous hospitalizations were learnt by asking whether they had been hospitalized before they were internalized in our hospital. Early hospitalizations were the ones that took place in one months' time and late hospitalizations were the hospitalizations before that. All patients were followed up by telephone for vital status two years from the date of discharge and overall mortality and 1-year and 2-year mortality rates and survival times were calculated.

We analyzed the peripheral venous bloods of these patients at the admission to the emergency room. Anemia was defined according to WHO criteria [11] as hemoglobin level <13 g/dl in men and <12 g/dl in women. Anemia is classified as normocytic if MCV was 80-100 fL, microcytic if MCV was <80 fL and macrocytic if MCV was >100 fL.

The study was approved by the Scientific Research and Thesis Evaluation Board of University of Health Sciences Suat Seren Chest Diseases and Surgery Education and Training Hospital (EPK TUEK, Date: 17.12.2018, number: E.13813). The study was in accordance with the ethical standards of the institutional committee. The study was retrospective and informed consent was not necessary. The patients' confidentiality is preserved.

Exclusion criteria

We excluded the patients who were under 18-years-of-age, had asthma, bronchiectasis, active tuberculosis, malignancy, or interstitial fibrosis.

Statistical analysis

Analyses of data were performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 22, software for Windows and data were presented as mean ± SD and numbers (n) and per cent (%). Student's *t*-test was conducted to compare the continuous variables between the groups and the χ^2 test for the comparison of categorical variables. The effect of anemia on overall survival was demonstrated by Kaplan-Meier analysis. The predictive values of the parameters for mortality were calculated with univariate and multivariate Cox regression analyses. The results were presented with 95% confidence intervals. The differences between the survival times of the groups were determined by Kaplan-Meier analysis and survival curves were compared by the Log-Rank test. In all analyses, $p<0.05$ was considered statistically significant.

Results

We analyzed hospital records of 300 consecutive patients with COPD who were internalized in our ward. 113 (37.7%) patients had anemia. Mean hemoglobin value was 13.3 ± 2.1 g/dl. 242 were (%80.7) men and 58 (19.3%) were women. 37 (12.3%) had microcytic, 73 (24.3%) had normocytic, three (1%) had macrocytic anemia. Demographics and clinical characteristics were presented in Table 1. One hundred and thirteen (113) patients (37.7%) had LTOT, 68 (22.7%) used NIMV and 66 (22%) used both LTOT and NIMV before admission; 39 patients (13.0%) were admitted to ICU. Table 2 shows the comparison of deceased and alive patients for clinical parameters. Overall survival time of our patients were 38.8±1.8 months (95% CI 35.3-42.3). Mean survival time of anemic patients was 31.9±2.9 months (95% CI 37.7-45.7) and mean survival time of normal patients was 41.7±2.1 months (95% CI 26.3-37.6) (p=0.001). Figure 1 shows Kaplan Meier curve analysis of all-cause overall survival times of anemic and normal patients. We analyzed the factors affecting survival time by using univariate and multivariate Cox regression analysis. In univariate analysis, age (HR= 1.08) (95% CI 1.02-1.05) (p<0.001), BMI (HR= 0.97) (95% CI 0.94-0.99) (p=0.024), the presence of anemia (HR= 1.75)

Table 1. Demographic and clinical characteristics.

Mean age (years) (min-max) (mean±SD)	(36 - 92) 67.9±10.4
Female/male	58 (19 %)/242 (81%)
Mean BMI (mean±SD)	26.6±6.8
Charlson comorbidity index (mean±SD)	4.0±1.5
FEV_1% (mean±SD)	37.3±16.5
FEV_1/FVC (mean±SD)	64.0±17.7
Hemoglobin (g/dl) (mean±SD)	13.3±2.1
Anemia/Normal n (%)	113 (37.7%)/187 (62.3%)
MCV (fL) (mean±SD)	85.7±9.6
MCHC (g/dl) (mean±SD)	32.4±3.6
Hemotocrit (%) (mean±SD)	41.2±6.3
Platelet ($\times 10^3/\mu L$) (mean±SD)	271.4±98.2
Eosinophil (n) (mean±SD)	0.1±0.2
CRP (mean±SD)	7.2±8.8
Serum creatinine (mean±SD)	1.0±0.4
ICU admission, n (%)	39 (13.0%)
Re-hospitalization, n (%)	174 (58.0 %)
Previous early (≤30 days) hospitalization, n (%)	49 (16.3%)
Previous late (> 0 days) hospitalization, n (%)	125 (41.7%)
Follow-up (months) (min - max) (mean±SD)	(0.2 - 66.0) 22.0±15.5

BMI, body mass index (kg/m^2); FEV_1%: forced expiratory volume in second 1%; FVC, forced vital capacity; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; CRP, C-reactive protein; ICU, intensive care unit.

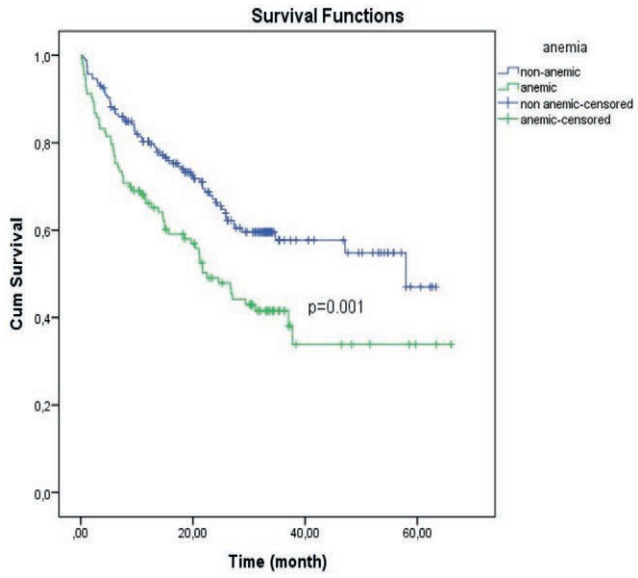

Figure 1. Overall survival (in months) of anemic and normal COPD patients (p=0.001) (number of anemic patients: 113; number of normal patients: 187).

(95% CI 1.23-2.74) (p=0.002), CCI scores (HR= 1.18) (95% CI 1.06-1.32) (p=0.003) and FEV_1% (HR: 0.99) (95% CI 0.98-0.99) (p=0.026) were factors affecting mortality. In multivariate analysis, anemia (HR= 1.48) (95% CI 0.99-2.19) (p=0.040), BMI (HR= 0.96) (95% CI 0.9 -0.99) (p=0.044) and FEV_1% (HR= 0.98) (95% CI 0.96-0.99) (p=0.002) remained as factors that affected mortality. Table 3 shows the univariate and multivariate analysis of the patients. We could not reach the spirometers of 24 patients and spirometries of six patients were not compatible with COPD, and therefore, we analyzed 270 patients. The patients were grouped according to their airflow limitation levels and were compared with respect to anemia for their survival time. Three (1%) patients were Group 1, 53 (20%) patients were Group 2, 106 (39%) patients were Group 3, 108 (40%) patients were Group 4. Mortality rates of the groups were presented in Table 4. Mortality rate of anemic Group 2 patients were significantly higher than normal Group 2 patients (p=0.001). However, mortality rates of anemic and normal patients were not different in Group 3 and 4 groups. Survival times of Group 2 normal and anemic patients were 31.6±5.8 (95% CI 20.2-43.1) and 55.5±3.6 (95% CI 48.4-62.6) (p=0.004) months respectively. Survival times of Group 3 normal and anemic patients were 38.4±3.5 (95% CI 31.6-45.3) and 37.6±4.6 (95% CI 28.7-46.5) (p=0.835) months respectively. Survival times of Group 4 normal and anemic patients were 37.6±3.1 (95% CI 31.5-43.7) and 27.1±4.0 (95% CI 19.2-35.1) (p=0.012) months respectively.

Table 2. Comparison of mortality and survival groups for clinical parameters.

	Mortality group (n=129)	Survival group (n=171)	p-value
Age (years)	70.4±10.3	66.0±10.1	<0.001
Sex			0.079
Female	19 (14.7%)	39 (22.8%)	
Male	110 (85.3%)	132 (77.2%)	
Charlson comorbidity index	4.2±1.5	3.8±1.6	0.047
BMI (kg/m^2)	25.6±6.6	27.3±6.8	0.041
FEV_1% (mean±SD)	34.4±14.7	39.4±17.4	0.014
FEV_1/FVC (mean±SD)	63.6±18.2	64.3±17.1	0.760
COPD severity groups			0.085
1	0 (0%)	3 (1.9%)	
2	17 (15%)	36 (22.9 %)	
3	43 (38.1%)	63 (40.1%)	
4	53 (46.9%)	55 (35.0%)	
Hemoglobin (g/dl) (mean±SD)	12.9±2.0	13.6±2.1	0.005
Anemia (%)			0.001
(+)	62 (48.1%)	51 (59.8%)	
(-)	67 (51.9%)	120 (70.2%)	
MCV (fL) (mean±SD)	84.2±12.0	86.7±7.2	0.028
MCHC (g/dl) (mean±SD)	32.3±5.3	32.4±1.3	0.946
Hemotoctrit (%) (mean±SD)	40.4±6.1	41.8±6.4	0.055
Platelet ($\times 10^3/\mu L$) (mean±SD)	271.9±104.2	271.0±93.7	0.938
Eosinophil (n) (mean±SD)	0.1±0.2	0.2±0.3	0.428
CRP (mean±SD)	6.2±7.8	7.9±9.4	0.102
Serum creatinine (mean±SD)	1.1±0.5	1.0±0.4	0.025
ICU admission (n) (%)	22 (17.2%)	17 (10.0%)	0.069
Re-hospitalization (n) (%)	92 (71.3%)	81 (47.6%)	<0.001
Previous early (≤30 days) hospitalization	31 (24.0%)	18 (10.6%)	0.002
Previous late (>30 days) hospitalization	62 (48.1%)	62 (36.5%)	0.044

BMI, body mass index (kg/m^2); FEV_1%: forced expiratory volume in second 1%; FVC, forced vital capacity; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; CRP, C-reactive protein

Kaplan-Meier survival curves of Group 2, 3, and 4 patients were presented in Figures 2, 3, and 4, respectively. Although Group 3 anemic patients had high mortality rates, there was no statistically significant difference. Survival times of anemic Group 2 and Group 4 patients were shorter.

Discussion

Anemia is a comorbidity associated with COPD severity and mortality. 37.7% of our patients had anemia. Factors affecting mortality were age, Charlson comorbidity index, BMI, FEV1%, anemia, MCV, hemoglobin, serum creatinin and early and late hospitalizations. Anemia (HR= 1.48) (p=0.040), BMI (HR= 0.96) (p=0.044) and FEV_1% (HR= 0.98) (p=0.002) affected survival. When patients were analyzed according to their spirometric severity by using FEV_1 values, mortality rate of anemic group 2 patients were significantly higher than anemic group 3 and 4 patients. Also, survival times of group 2 and group 4 anemic patients were shorter than normal COPD patients. To the contrary to classical knowledge, recent studies have shown that anemia rates are high (7.5-

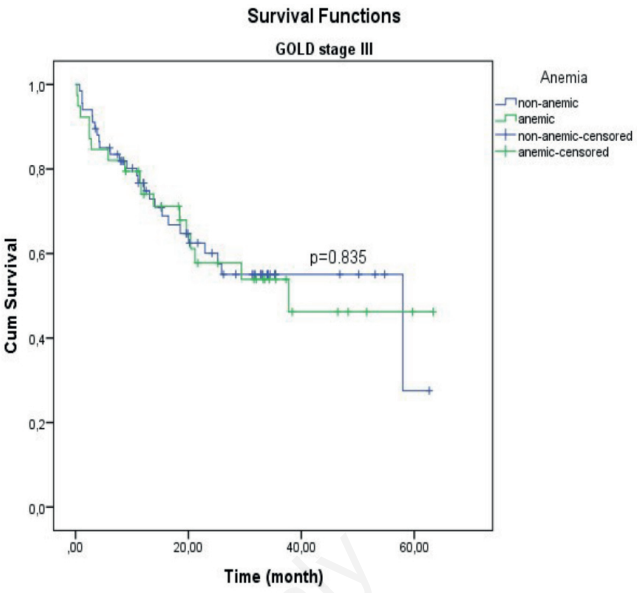

Figure 3. Survival (in months) of Group 3 COPD patients with and without anemia (p=0.835) (number of patients with anemia: 39; number of normal COPD patients: 41).

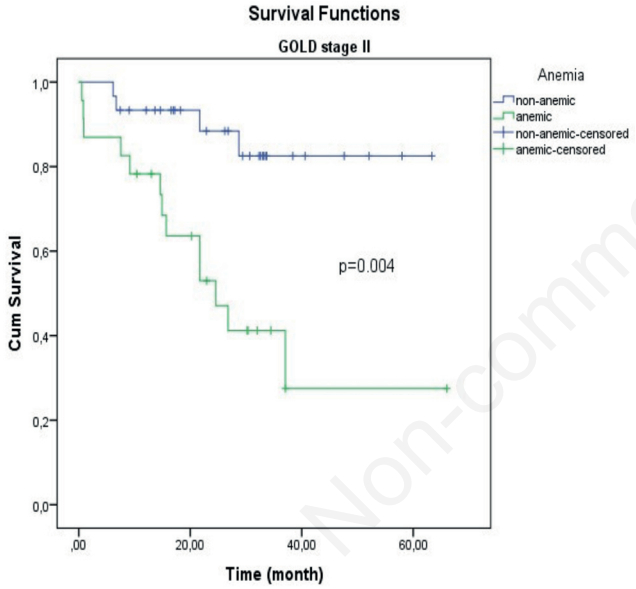

Figure 2. Survival (in months) of Group 2 COPD patients with and normal patients (p=0.004) (number of patients with anemia: 26; number of patients without anemia: 30).

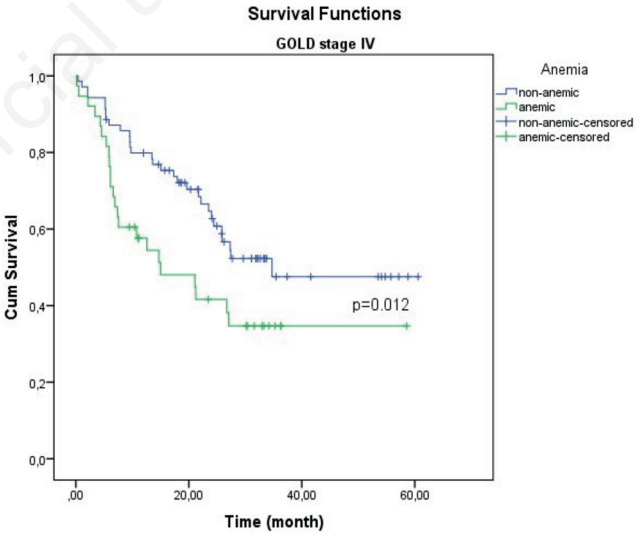

Figure 4. Survival (in months) of Group 4 COPD patients with and without anemia (p=0.012) (number of patients with anemia: 38; number of patients without anemia: 70).

Table 3. Evaluation of clinical parameters affecting survival in patients with COPD; Cox regression analysis.

	Univariate analysis				Multivariate analysis			
	Beta	OR	95% CI	p-value	Beta	OR	95%CI	p-value
Age	0.035	1.08	1.02-1.05	<0.001	0.030	1.30	1.00-1.06	0.051
BMI	-0.003	0.97	0.94-0.99	0.024	-0.031	0.96	0.94-0.99	0.044
Anemia (+) *vs* (-)	0.559	1.75	1.23-2.74	0.002	0.390	1.48	0.99-2.19	0.040
CCI scores	0.169	1.18	1.06-1.32	0.003	0.060	1.06	0.85-1.32	0.593
FEV_1%	-0.013	0.99	0.98-0.99	0.026	-0.022	0.98	0.96-0.99	0.002

BMI, body mass index (kg/m^2); FEV_1%: forced expiratory volume in second 1%.

30%), and polycythemia is rare (6%) in COPD patients [1]. Hemoglobin level is associated with increased dyspnea and mortality [12]. Normochromic normocytic anemia occurs in COPD and is thought to be due to resistance to the action of erythropoietin [13]. It is still a matter of debate whether anemia itself contributes to the pathology and progression of inflammatory diseases or if the poorer prognosis of patients with inflammatory disorders plus anemia compared with inflammatory disorders alone is merely a reflection of a more advanced disease (i.e., association rather than causation). Anemia in inflammatory diseases is complex and multifactorial, and it may be challenging to separate out the component due to anemia. Also, it can be epiphenomenon.

COPD is an inflammatory disease that is accompanied by numerous comorbidities. COPD has a higher prevalence of many concomitant diseases [14]. However, the relationship between anemia and the severity of COPD has only been studied in a few studies, and the results are conflicting. Yang claims that the risk of anemia and cancer is unrelated to a decline in lung function. They go on to say that a decline in lung function is an independent risk factor for an increase in all-cause mortality [14]. Another study found that the overall prevalence of anemia is 27%, with no correlation between the severity of COPD and anemia [15]. According to the third study, anemia is seen in 14% of the patients, and the prevalence of anemia increases with the severity of COPD [16]. Although it has been reported that anemia affects 7.5-33% of COPD patients [1], the prevalence of anemia (37.7%) and mortality rates of our anemic COPD patients were higher (Table 3). There were various reasons of this high prevalence. It is known that prevalence of anemia increases with age [17] and COPD is a disease which affects the aging population. Therefore, anemia in COPD may also be related to the aging process [1]. Our study supported previous results about age. Our patients were old and severe patients. Our mean mean age was 67.9 years and FEV_1% was 37.3%. Although mortality was higher in older patients, age did not remain significant as a parameter that was effective for mortality when multivariate analysis was performed. Some of the comorbidities in COPD may result in anemia. For example, anemia prevalence is reported to be 15% in patients with heart failure [18]. Also, anemia is common in chronic renal failure. Therefore, it is advisable to screen for confounding factors in anemic patients with COPD [19]. Menau showed that Charlson comorbidity index was higher in anemic group and comorbidity index was the only predictive factor of anemia [20]. Therefore we used the Charlson comorbidity index to analyze comorbidities and, in our study, patients who died had higher Charlson comorbidity indexes and serum creatinine levels; however, these parameters did not remain as significant factors affecting survival. Anemia is a risk factor for readmission to hospital in patients with COPD. Barba [21] reports a 25% higher risk of readmission in anemic COPD patients. Yu [22] reports a 7.3% unplanned early readmission rate. In our study, previous early and late hospitalizations were higher in deceased COPD patients. This high rate was due to the severity of airflow limitation.The relationship between anemia and survival time in COPD has been analyzed in previous studies. These studies have contradictory results. Boutou [23] shows that survival time of anemic COPD patients is shorter, independent of age and FEV_1%. Their median survival time is 68.7 months. Cote [8] reports median survival time as 49 months. Martinez studies patients with COPD acute exacerbation and finds a shorter mean survival time which is 339 days (about 11.3 months) [24]. Kassim [25] shows that among adults with sickle cell anemia, decreased FEV1% predicted was associated with earlier death (HR per % predicted 1.02; 95% CI 1.00-1.04; p=0.037). Older age (HR= 1.07; 95% CI 1.04-1.10; p<0.001) was also associated with increased hazard ratio of death. In our study we had patients with COPD acute exacerbation. Median survival time of our anemic patients was 22.5 months. Our patients had COPD acute exacerbation which resulted in respiratory failure and were severe. Mean FEV_1% of our patients was 37.3 and 79% of our patients were Group 3 and 4 COPD severity. Most of them needed NIMV in the ward and 13% were transferred to ICU. There is limited data about the relationship between COPD severity and anemia. Menou [20] states that anemia is not influenced by GOLD stage. Boutou [9] performs a study with stable COPD patients and reports anemia in older patients and in COPD patients with lower FEV_1% (42.3±9.8 vs 50.7±6.1; p<0.05) and more severe disease according to GOLD classification (stage 2 = 24.1% vs 29.9%; stage 3 = 44.8% vs 46.6% and stage 4 = 31% *vs* 23.2%; p<0.05). There are similar results in the study from Northern India [10]. They report more anemic patients in GOLD Stage 3 and 4 COPD groups, but mortality rates and survival time are not mentioned. In our study, anemia was correlated with COPD severity, and it affected mortality and survival time of COPD patients. We found that mortality rate of anemic group 2 patients was higher and survival time of anemic group 2 and stage 4 patients were lower. We had expected to find that as COPD severity increased, survival time of anemic patients would decrease, and mortality would increase. Although there was a tendency parallel to our expectations, we found that anemic patients with group 2 severity had worse mortality outcomes. When we analyzed their comorbidities, we found that group 2 anemic patients had more comorbidities than other stages, which might explain worse mortality rates. Although patients had better spirometer values, they had comorbidities which resulted in hospitalization of these patients and worse mortality outcomes. Their survival times were lower. Low survival times of group 4 anemic patients could be explained with their low respiratory function reserves. As regards the limitations of our study we had limited number of patients. When they were divided into subgroups, number of patients in each group reduced. The number of patients in each category is limited (e.g., only three are Group 1). Although we included patients who were hospitalized in the ward for COPD acute exacerbation resulting in respiratory failure, their spirometry's were performed when they were stable. Also, we did not assess all comorbidities, because we used Charlson comorbidity index and ana-

Table 4. Mortality rates of COPD patients with and without anemia according to their groups.

	Group 1 (n=3)		Group 2 (n=53)		Group 3 (n=106)		Group 4 (n=108)	
	Mortality	Survival	Mortality	Survival	Mortality	Survival	Mortality	Survival
Anemia (+)	-	-	13 (56.5%)	10 (43.5%)	17 (43.6%)	22 (56.4%)	23 (60.5%)	15 (39.5%)
Anemia (-)	0 (0.0%)	3 (100.0%)	4 (13.3%)	26 (86.7%)	26 (38.8%)	41 (61.2%)	30 (42.9%)	40 (57.1%)
p-value	-		0.001		0.629		0.079	

lyzed the comorbidities in this index. Also, the changes in hemoglobin concentration during follow-up were not captured. There was missing data due to the retrospective design of the study. We analyzed our patients in terms of FEV_1% and did not take exacerbation and dyspnea scores into consideration, because their dyspnea scores were not recorded in their files. If we had analyzed them according to A-B-C-D groups and considered exacerbation status, all of them would be group C or D due to the hospitalization status. Further studies can be performed about COPD GOLD groups and anemia. We considered subgroups by using spirometries. However, as thorax CT's were not available in all patients, we could not evaluated the impact of different COPD types, such as bronchiolitis or emphysema. Also, we did not consider exacerbation causes.

Conclusions

Anemia prevalence of our COPD patients is 37.7%. They are older and have a greater number of comorbidities. Their 1-year and 2-year overall mortality rates are higher. The factors influencing mortality were BMI, anemia, and FEV_1%.When COPD patients are grouped according to their severity, our anemic Group 2 patients have a higher mortality rate than patients in Groups 3 and 4. This could be the result of comorbidities. Additionally, our Group 2 and Group 4 anemic patients have shorter survival times. To clarify the relationship between COPD GOLD groups, anemia, and comorbidities, additional, more in-depth research should be conducted.

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