Original Article

Anemia as a clinical marker of stable chronic obstructive pulmonary disease in the Korean obstructive lung disease cohort

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Background: Anemia is a major co-morbidity in chronic obstructive pulmonary disease (COPD). However, the mechanism of development for anemia and the impact of anemia on the prognosis of COPD remain poorly understood. Therefore, this study attempted to evaluate the prognostic role of anemia on the clinical course of COPD and investigate the factors linked with the serum hemoglobin level in COPD.

Methods: We analyzed 407 COPD patients enrolled in the Korean obstructive lung disease (KOLD) cohort at 16 hospitals in Korea recruited over 9 years. Multivariate Cox regression analysis was performed to find independent predictors of survival and multivariate logistic regression analyses were done to find independent factors.

Results: Anemic COPD were older with lower body mass index (BMI) (P<0.001), lower serum cholesterol level (P=0.001), lower serum albumin level (P<0.001), and shorter 6-minute walking distance (P=0.046) compared to non-anemic COPD. A multivariate Cox regression analysis revealed that age (P=0.002), BMI (P=0.001), post-bronchodilator forced expiratory volume in 1 second (FEV_1) (P=0.007), 6-minute walk distance (P=0.008), anemia (P=0.025) were significant predictors for all-cause mortality. In multivariate regression analysis, older age (P<0.001), female gender (P=0.001), lower BMI (P=0.016), and lower serum albumin level (P<0.001) were independent factors associated with lower serum hemoglobin level.

Conclusions: Our data showed that anemia was an independent risk factor for mortality in COPD, and aging, lower serum albumin level, and lower BMI were independent factors associated with lower serum hemoglobin level.

Keywords: Chronic obstructive pulmonary disease (COPD); anemia; clinical marker

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Introduction

Chronic obstructive pulmonary disease (COPD) will be the 3rd leading cause of death in North America, and a national survey conducted in Korea showed the prevalence of COPD under the definition of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) criteria was of 17.2% (men, 25.8%; women, 9.6%) for subjects older than 45 years (1,2).

Patients with COPD suffer from many concurrent comorbidities, some of which are deemed to be major causes of death in COPD (3). Anemia is one of the co-morbidities and is an independent risk factor for mortality in a subset of COPD patients (4,5). Correcting anemia can improve dyspnea by decreasing the work required for breathing and minute ventilation in COPD (6,7).

Previous studies have suggested that chronic inflammation is the main mechanism whereby anemia can develop in COPD, although the causes of anemia are thought to be multifactorial (8,9). Nevertheless, the mechanism of development for anemia and the impact of anemia on the prognosis of COPD remain poorly understood. Hence, this study was performed to search factors linked with anemia and to evaluate the role of anemia on the prognosis of COPD.

Methods

Study design

Patients & definition of each condition

We enrolled 407 COPD patients of the Korean obstructive lung disease (KOLD) prospective cohort who attended pulmonary clinics in 16 university affiliated hospitals on an outpatient basis from 3 provinces throughout Korea (246 patients from Seoul, 130 patients from Gyunggi-do, 31 patients from Gangwon-do) from June 2005 to January 2015 (*Figure 1*). Out of 957 patients who were referred for evaluation and management of airway disease before enrollment, 453 patients with asthma according to clinician's discretion and 97 patients with non-smoking COPD were excluded from this study (*Figure 1*). Inclusion criteria of COPD were as follows: (I) age ≥40 years; (II) current or former smoker with a smoking history ≥10 pack-years; (III) post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) <0.7; (IV) no or minimal abnormality on a chest radiography.

Patients with heart failure, coronary artery disease, tuberculous destroyed lung, severe bronchiectasis, pneumoconiosis, lung cancer, home oxygen therapy, or pure asthma were excluded based on the judgement of physicians.

For this cohort, we have followed the patients every 3 months and mean follow up period was 4.9±3.1 years.

Anemia was determined by initial serum hemoglobin level according to the reference values of hemoglobin: <12 g/dL for women and <13 g/dL for men (10).

Acute exacerbation was graded from mild to severe as previously reported during the 1-year follow up period after enrollment and only moderate and severe exacerbations were included in the exacerbation group (11). Frequent exacerbators were determined as previously defined (1,11).

This study was approved by the institutional review board of the Asan Medical Center (Approval No. 2005-0345) and the other 15 hospitals. Written informed consent was obtained from all patients.

Clinico-physiological indices of COPD

Demographic and clinical data, including age, sex, smoking status, history of exacerbations, pulmonary function tests, etc., were obtained at enrollment. Blood samples, collected at enrollment when the patients were stable, were used for laboratory tests. The body mass index (BMI) was calculated as the body weight divided by the height squared (kg/m^2). Dyspnea was assessed using the Modified Medical Research Council (mMRC) Dyspnea Scale, and the health-related quality of life was assessed using the St. George Respiratory Questionnaire (SGRQ).

Six-minute walk test was conducted, according to the ATS statement (12).

Spirometry was performed using Vmax 22 (SensorMedics, Yorba Linda, CA, USA) and PFDX (MedGraphics, St. Paul, MN, USA) according to the American Thoracic Society guidelines (13). The spirometry reference values were based on the Korean equation (14). Post-bronchodilator spirometry values were measured 15 minutes after administering 400 μg of salbutamol. Lung volumes, including the total lung capacity (TLC) and residual volume (RV), were measured using body plethysmography which were V6200 (CareFusion, San Diego, CA, USA), PFDX, or Vmax 22 (15). The diffusing capacity of carbon monoxide (D_{LCO}) was measured by assessing the single-breath carbon monoxide uptake (Vmax 22 or PFDX) (16).

Chest computed tomography (CT) indices for COPD assessment

The emphysema index, CT air-trapping index, and airway dimensions were determined from chest CT data, as previously reported (17,18). To measure these

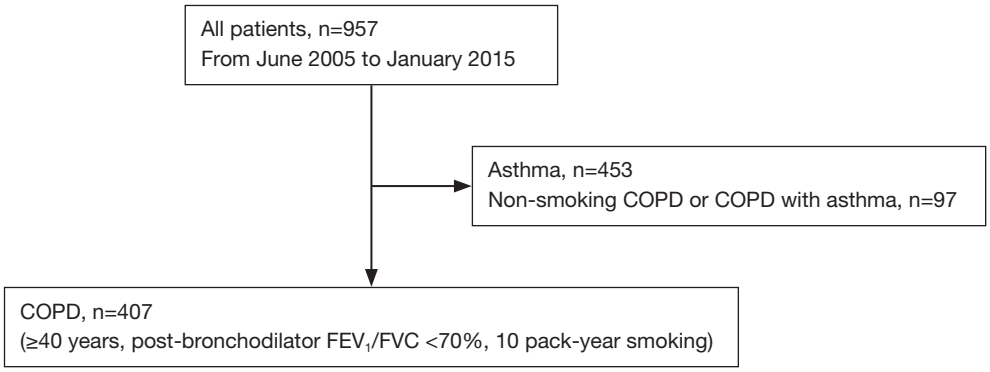

Figure 1 Flow diagram of enrollment. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

indices, patients underwent volumetric CT scans at full inspiration and expiration with a 16-MDCT scanner (the CT machines came from three manufacturers including the Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany; the GE Lightspeed Ultra, General Electric Healthcare, Milwaukee, WI, USA; and the Philips Brilliance 16, Philips Medical Systems, Best, Netherlands).

Statistical analysis

All data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA), and all values were expressed as means ± standard deviation except for the survival period described as means ± standard error. Chi-Square test or Fisher's exact test was performed for categorical data and Student's *t*-test was used for continuous data. A P value less than 0.05 was considered statistically significant.

A Kaplan-Meier analysis with a log-rank test was conducted to evaluate the survival. A Cox proportional hazard regression analysis was carried out to find the significant variables associated with the survival. A Cox regression of the log hazard ratio (HR) on a covariate with a standard deviation of 0.50 based on a sample of 407 observations achieved 82% power at a 0.05 significance level.

Multiple logistic regression analyses were performed to choose the significant variables of the preceding analyses. The demographic variables, indicating the sample profile information including age and sex, and clinically meaningful variables are included in the multiple logistic regression. To avoid multicollinearity, the variables were included in multiple regression analyses when the variance inflation factor was less than 10.

Results

Baseline characteristics

Our COPD cohort were male-dominant (male =97.3%, n=396), and 7.1% (n=29) of the entire group had anemia [mean cell volume (MCV) =93.6±5.0 fL, 96.6% (28/29) = normocytic anemia (MCV =80–100 fL), 3.4% (1/29) = macrocytic anemia (MCV ≥100 fL)]. The characteristics of the entire cohort included a mean age of 67.0±7.5 years, mean FEV_1 of 49.1±15.5 (pre-bronchodilator) and 54.3%±16.0% (post-bronchodilator).

Compared to the non-anemic COPD group, the patients of the anemic COPD group were significantly older (P<0.001) and had lower BMI (P=0.005), lower serum albumin levels (P<0.001), and lower serum cholesterol levels (P=0.001) (*Table 1*). On the other hand, inflammatory markers such as the leukocyte count and high-sensitivity C-reactive protein (hs-CRP) level were not different between the two groups (*Table 1*).

Radiological evaluations and pulmonary function tests including FVC, FEV_1, FEV_1/FVC, D_{LCO}/VA (alveolar volume), D_{LCO}, RV/TLC, and inspiratory capacity (IC)/TLC were not different between the two groups (*Table 2*). However, the 6-minute walk distance was shorter in the anemic COPD group (P=0.046) (*Table 2*).

Survival analyses

Of the 58 patients with COPD who died during the observation period, death was most frequently due to pneumonia (6 patients), respiratory failure (6 patients), acute exacerbation of COPD (6 patients), lung cancer (6 patients), cancers other than lung cancer (9 patients).

Table 1 Baseline characteristics of the patients with COPD

Variables	Anemic COPD	Non-anemic COPD	P value
Total number	29	378	
Age (years)	73.1±6.9	66.5±7.4	<0.001
Gender (male) (%)	96.6 (28/29)	84.4 (368/378)	0.561
Smoker (pack-years)	39.3±19.6	47.1±26.7	0.125
BMI (kg/m^2)	21.4±2.9	23.1±3.2	0.005
SGRQ	31.8±15.8	32.9±17.9	0.757
mMRC	1.63±1.33	1.66±1.06	0.900
Charson index	1.41±0.98	1.17±0.55	0.196
Serum laboratory finding			
Leukocyte (×10^3/μL)	6.6±1.7	7.3±2.0	0.067
hs-CRP (mg/dL)	0.31±0.36	0.40±1.04	0.710
Hemoglobin (g/dL)	12.2±0.7	15.0±1.1	<0.001
Platelet (×10^3/μL)	259.9±80.8	238.6±62.3	0.090
Protein (g/dL)	6.96±0.51	7.11±0.50	0.131
Albumin (g/dL)	3.94±0.41	4.27±0.30	<0.001
Cholesterol (mg/dL)	164.8±30.2	188.6±36.4	0.001
Creatinine (mg/dL)	1.04±0.31	1.04±0.18	0.934

Data are represented means ± standard. COPD, chronic obstructive pulmonary disease; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; mMRC, modified Medical Research Council Dyspnea Scale; SGRQ, St. George Respiratory Questionnaire.

Other causes were myocardial infarction (3 patients), respiratory failure after surgery (2 patients), septic shock (2 patients), pneumothorax (1 patient), liver cirrhosis (1 patient), multiorgan failure (1 patient) and suicide (1 patient). Since the cause of death was unidentified for 24.1% (14/58) of the instances, only all-cause mortality was used for the survival analyses.

A Kaplan-Meier analysis showed that patients with non-anemic COPD (mean survival period =8.88±0.15 years) survived longer than those with anemic COPD (mean survival period =6.77±0.84 years, P<0.001) (*Figure 2*).

The multivariate analysis conducted with the Cox regression method including age, gender, mMRC, BMI, post-bronchodilator FEV_1, 6-minute walk distance, and anemia revealed that age (HR =1.083, P=0.002), BMI (HR =0.840, P=0.001), post-bronchodilator FEV_1 (HR =0.969, P=0.007), 6-minute walk distance (HR =0.995, P=0.008), and anemia (HR =2.591, P=0.025) were significant predictors of all-cause mortality (*Table 3*).

Factors associated with serum hemoglobin level

Multivariate logistic regression analysis using significant factors obtained from univariate analyses (*Table 4*) demonstrated that the independent factors associated with a lower serum hemoglobin level were a lower serum albumin level (t=5.902, P<0.001), older age (t=−4.087, P<0.001), male gender (t=3.326, P=0.001), and lower BMI (t=2.602, P=0.010), in the order of highest relation (*Table 4*). However, post-bronchodilator FEV_1, D_{LCO}, and the 6-minute walk distance were not independently associated (*Table 4*).

Discussion

The aim of our study was to investigate whether anemia can predict the survival of COPD and to search for factors that are independently associated with serum hemoglobin level in COPD. We found that anemia was a significant factor associated with the survival of COPD in the Cox regression analysis. Our data also demonstrated that nutritional factors, including a lower serum albumin level and lower BMI along with an increasing age and female gender were independent risk factors associated with a lower serum hemoglobin level in COPD, suggesting that aging and malnutrition are linked with anemia in COPD.

Our study has a number of interesting findings. First, our data showed that anemia was an independent factor to predict the survival of stable COPD in KOLD cohort. Previous studies with various cohorts reported that anemia is associated with a reduced survival in COPD (5,19-21). In the cohorts with stable COPD recruited on an outpatient basis, anemia has not been proven to be a risk factor for mortality through multivariate analysis, even though the survival period was reported to be shorter in anemic COPD, or hematocrit was significantly higher in the COPD patients who survived (19,20). However, in cohorts with severe COPD including COPD patients receiving long-term oxygen therapy and patients hospitalized for acute exacerbation, hematocrit or the presence of anemia was an independent predictor of survival (5,21).

As shown in the method, our cohort excluded COPD with cardiac comorbidities, tuberculous destroyed lung, severe bronchiectasis, pneumoconiosis, or lung cancer, because we attempted to observe the pure clinical course of COPD without the hindrance of those confounding

Table 2 Physiological and radiological findings of patients with COPD

Variables	Anemic COPD	Non-anemic COPD	P value
Pulmonary function after bronchodilator (%)			
FVC	85.3±13.6	83.4±16.2	0.543
FEV_1	58.5±16.7	54.0±16.0	0.147
FEV_1/FVC	47.2±11.9	46.7±11.0	0.818
D_{LCO} (%) [n]	72.2±15.8 [27]	77.9±24.4 [347]	0.095
D_{LCO}/VA (%) [n]	72.3±22.4 [26]	78.6±23.9 [341]	0.197
RV/TLC (%) [n]	48.8±11.5 [26]	45.2±13.1 [351]	0.170
Six-minute walk test			
6MWD (m) [n]	394.3±19.6 [26]	429.2±85.7 [364]	0.046
Resting O_2 Sat (%) [n]	97.0±1.1 [26]	96.4±1.8 [364]	0.089
Minimum O_2 Sat (%) [n]	95.5±2.1 [26]	94.6±4.9 [364]	0.345
Radiological findings			
Emphysema index [n]	22.4±17.8 [21]	21.7±15.5 [351]	0.416
Wall area (%) [n]	65.7±5.4 [21]	66.6±5.0 [351]	0.420
Air-trapping index (%) [n]	0.94±0.04 [21]	0.95±0.03 [351]	0.235
Frequent exacerbators (%)	35	24.7	0.313

The number of participants is noted in square brackets, if any values for each item were missing. COPD, chronic obstructive pulmonary disease; D_{LCO}/VA, diffusing capacity for carbon monoxide /alveolar volume; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; O_2 Sat, oxygen saturation; 6MWD, 6-minute walk distance; RV, residual volume; TLC, total lung capacity; Wall area (%), wall area/(wall area + lumen area) ×100; Air trapping index (%), ratio of the mean lung density on expiration and inspiration ×100.

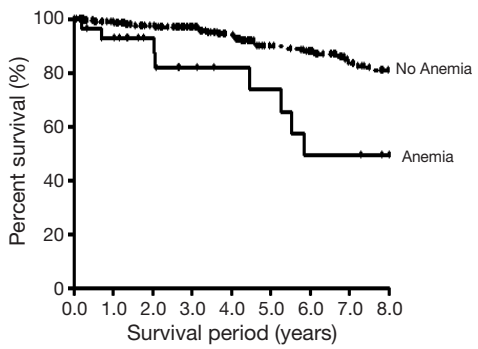

Figure 2 Survival analysis of non-anemic COPD (mean survival = 8.88±0.15) and anemic COPD (mean survival =6.77±0.84 years) by the Kaplan-Meier method (P<0.001). COPD, chronic obstructive pulmonary disease.

variables.

It is no wonder that our cohort had a lower prevalence of anemia (7.1%) since patients with milder COPD and higher FEV_1 were enrolled in KOLD cohort, compared to severe COPD cohorts as in previous research (mean FEV_1 of 34% for men and 37% for women and an anemia rate of 12.6% for men and 8.2% for women reported by Chambellan *et al.*, and mean FEV_1 of 37.4% and anemia rate of 33% reported by Martinez-Rivera *et al.* (5,21).

A recent report by Ahn *et al.* identified serum hemoglobin levels and left ventricular ejection fraction along with a lower FEV_1 as independent risk factors for mortality in COPD patients who underwent comprehensive cardiac evaluations (4). Although pulmonary function in the cohort reported by Ahn *et al.* (60.2%±18.7% of mean post-bronchodilator FEV_1) was better than that of our cohort, their cohort is different from ours since their cohort recruited COPD patients with a higher prevalence of cardiac co-morbidities who simultaneously visited a cardiology clinic and a pulmonology clinic (4).

Previous reports indicated the possibility for the correction of anemia to improve the functional outcomes of COPD by decreasing dyspnea and the work during breathing (6,7). However, further research on COPD is required to determine the relationship between anemia correction and long-term outcomes.

Table 3 Prognostic factors for the mortality in total COPD group by Cox regression analysis

Variables	Univariate model		Multi-variate model	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age (years)	1.142 (1.092–1.194)	<0.001	1.083 (1.030–1.139)	0.002
Gender (male)	1.592 (0.220–11.535)	0.645	1.006 (0.132–7.692)	0.995
BMI (kg/m^2)	0.758 (0.694–0.824)	<0.001	0.840 (0.767–0.920)	0.001
Anemia	3.755 (1.835–7.686)	<0.001	2.591 (1.125–5.952)	0.025
Serum albumin (g/dL)	0.304 (0.127–0.727)	0.007	–	–
Serum chol. (mg/dL)	0.932 (0.992–1.009)	1.000	–	
Pulmonary function test				
Post BD FVC (%)	0.967 (0.950 – 0.983)	<0.001	–	–
Post BD FEV_1 (%)	0.945 (0.925–0.964)	<0.001	0.969 (0.947–0.991)	0.007
D_{LCO} (%)	0.969 (0.958–0.980)	<0.001	–	–
RV/TLC (%)	1.060 (1.037–1.084)	<0.001	–	–
Six-minute walk test				
6MWD (m)	0.990 (0.988–0.993)	<0.001	0.995 (0.992–0.999)	0.008
Resting O_2 Sat (%)	0.979 (0.839–1.144)	0.792	–	–
Minimum O_2 Sat (%)	0.937 (0.902–0.972)	0.001	–	–
Frequent exacerbators	1.218 (0.913–1.624)	0.180	–	–

All variables were analyzed using univariate and multivariate Cox regression models. COPD, chronic obstructive pulmonary disease; BMI, body mass index; D_{LCO}, diffusing capacity for carbon monoxide; post BD FEV_1, post-bronchodilator forced expiratory volume in 1 second; FVC, forced vital capacity; O_2 Sat, oxygen saturation; 6MWD, 6-minute walk distance; RV, residual volume; TLC, total lung capacity.

Second, compared to non-anemic COPD, anemic COPD of the KOLD cohort had some distinct clinical features including a lower BMI, shorter 6-minute walking distance, lower albumin level and lower cholesterol level whereas inflammatory markers such as leukocyte count and hs-CRP did not exhibit differences between the two groups. A multivariate analysis showed that nutritional factors including a lower serum albumin level, lower BMI along with old age and gender were independent factors associated with the serum hemoglobin level in COPD, suggesting aging and malnutrition are linked with anemia in COPD.

It is not clear yet whether anemia in COPD is a part of the aging process independent of COPD progression or if it develops as a comorbidity of COPD.

Previous studies have reported that anemia mainly develops due to chronic inflammation in COPD because the low-grade systemic inflammation is associated with an increased risk of major co-morbidities in COPD, irrespective of smoking (9,22). However, multiple factors have been suggested to cause anemia in COPD in addition to systemic inflammation, including an increasing age, malnutrition, renal dysfunction, and the use of certain medicines such as theophylline and angiotensin-converting enzyme inhibitor (9,23).

Our data showed that inflammatory markers were not associated with the serum hemoglobin level, and this difference may be attributed to the fact that our cohort had milder COPD patients with a higher FEV_1 enrolled from a stable cohort, when compared to previous studies (5,8).

The low body weight commonly found in COPD can weaken lung function and can reduce exercise capacity (24). Small studies identified dietary modulation as a promising intervention, and there is growing evidence that nutritional supplementation can improve body weight, respiratory muscle strength, and quality of life (24,25). However, nutritional intervention to improve the prognosis of COPD should be further validated in future studies.

We also acknowledge several limitations of this study.

Table 4 Independent factors associated with serum hemoglobin level by multivariate linear regression method

Variables	B	SE	Beta	t	P value
Univariate analysis					
Age (years)	−0.056	0.008	−0.318	−6.746	<0.001
R-square =0.318, adjusted R-square =0.101, F=45.515, P<0.0001					
Gender (male)	1.262	0.379	0.156	3.343	0.001
R-square =0.477, adjusted R-square =0.227, F=14.367, P<0.0001					
BMI (kg/m^2)	0.061	0.021	0.145	2.955	0.003
R-square =0.021, adjusted R-square =0.019, F=8.733, P=0.003					
Post BD FEV_1 (%)	−0.005	0.004	−0.055	−1.110	0.268
R-square =0.003, adjusted R-square =0.001, F=1.232, P=0.268					
D_{LCO} (%)	−0.003	0.003	−0.052	−1.006	0.315
R-square =0.003, adjusted R-square =0.000, F=1.013, P=0.315					
Serum albumin (g/dL)	1.427	0.195	0.345	7.307	<0.001
R-square =0.119, adjusted R-square =0.117, F=53.395, P<0.0001					
6MWD (m)	0.002	0.001	0.160	3.190	0.002
R-square =0.026, adjusted R-square =0.023, F=10.176, P=0.002					
Multivariate analysis					
Age (years)	−0.038	0.009	−0.216	−4.087	<0.001
Gender (male)	1.262	0.379	0.160	3.326	0.001
BMI (kg/m^2)	0.056	0.021	0.135	2.602	0.010
Post BD FEV_1 (%)	−0.008	0.004	−0.099	−1.827	0.069
D_{LCO} (%)	−0.006	0.003	−0.099	−1.844	0.066
Serum albumin (g/dL)	1.107	0.201	0.274	5.494	<0.001
6MWD (m)	0.001	0.001	0.051	0.914	0.361
R-square =0.477, adjusted R-square =0.227, F=14.367, P<0.0001					

B, regression parameter; SE, standard error; BMI, body mass index; D_{LCO}, diffusing capacity for carbon monoxide; post BD FEV_1, post-bronchodilator forced expiratory volume in 1 second; 6MWD, 6-minute walk distance.

First, since the number of anemic patients was only 7.1% of our cohort, further validation of our observations seems to be necessary with a larger cohort. Second, our COPD cohort had male-dominant feature, since smoking is more prevalent in male in Korean population. Third, this study cannot determine a causal link between anemia and the associated factors. Fourth, the COPD assessment test score was not analyzed because it was not obtained at the initial enrollment. Fifth, the history of medication in our analysis was not taken into consideration because the current study was not a randomized controlled trial. Sixth, general population of Korea may not be represented by our subjects considering the feature of our men-dominant cohort and enrollment from three out of ten provinces of Korea.

Conclusions

In conclusion, our data suggested that in COPD, anemia was an independent risk factor for mortality, and nutritional factors such as a lower serum albumin level and lower

BMI were independent factors associated with a lower hemoglobin level.

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Footnote

Conflicts of Interest: CK Rhee reports personal fees from MSD Korea, personal fees from AstraZeneca, personal fees from Novartis, personal fees from Mundipharma, personal fees from Boehringer-Ingelheim, outside the submitted work. YM Oh received payment for lecturing from MSD Korea, AstraZeneca Korea, Boehringer Ingelheim Korea, Novartis, DongWha, Takeda, and GSK Korea. SD Lee received support from Takeda Pharmaceuticals International GmbH for travel to an investigator meeting. He received payment from Takeda Pharmaceuticals International GmbH for attendance at an advisory board. He also received honoraria from GlaxoSmithKline, AstraZeneca, and Boehringer Ingelheim. The other authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of the Asan Medical Center (Approval No. 2005-0345) and the other 15 hospitals. Written informed consent was obtained from all patients.

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