Cardiac Co-morbidities in Chronic Obstructive Pulmonary Disease

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- ABSTRACT -

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Background: Coronary artery disease (CAD) is a frequent co-morbidity in chronic obstructive pulmonary disease (COPD) and cardiovascular disease is the most common cause of death in COPD. Therefore, this study was performed to identify the prognostic factors associated with the CAD in COPD and investigate the independent risk factors for mortality in COPD patients who underwent comprehensive cardiac evaluations

Methods: We retrospectively reviewed 405 patients with COPD who had undergone comprehensive cardiac evaluations including coronary angiography, coronary multi-detector computed tomography and echocardiography in Ajou University Hospital from Jan 2000 to Dec 2012. Survival analyses of prognostic factors were performed in this retrospective cohort.

Results: Male gender, hypertension, left heart failure, lower hemoglobin level, and lower serum HDL were independently associated with the presence of CAD in COPD ($p<0.05$). Older age, lower body mass index(BMI), lower left ventricular ejection fraction, lower forced expiratory volume in one second($FEV_{1)}$, and lower hemoglobin level were independently associated with higher mortality in total COPD group ($p<0.05$), whereas presence of CAD was not.

Conclusion: Our study identified lower left ventricular ejection fraction and lower hemoglobin level along with older age, lower BMI, and lower FEV_1 as independent risk factors for the mortality of COPD patients, suggesting that multidisciplinary approaches are required in the care of COPD patients. Male gender, hypertension, left heart failure, and lower serum HDL level were independent predictors for the presence of CAD in COPD.

Keywords: Chronic obstructive pulmonary disease (COPD), coronary artery disease, mortality

TABLE OF CONTENTS

I. Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing cause of morbidity and mortality worldwide [1]. COPD is now recognized not as a single disease, but a syndrome with multiple phenotypes accompanied by many co-morbidities [2, 3]. Cardiovascular disease among the many co-morbidities of COPD is the main cause of death for COPD and atherosclerosis may occur in COPD regardless of smoking history [4-6].

Oxidative stress, proteolytic enzymes, inflammatory cytokines, and molecules related to the aging process are thought to contribute to the development of coronary artery disease (CAD) in COPD [7-12]. Clinically, the degree of emphysema and airflow limitation are reported to be associated with the development of CAD in COPD [13-15]. There is strong epidemiologic evidence that reduced lung function is a marker for cardiovascular mortality independent of age, gender, and smoking history [15]. However, clinical risk factors associated with CAD in patients with COPD are not easy to identify, since the data of angiography proven CAD in COPD are extremely difficult to obtain [16, 17]. So far, few reports clearly defined COPD without CAD as a control because angiography was not done in all the patients with COPD, although some studies did investigate the clinical course of COPD with CAD [18, 19].

Therefore, this study was performed to identify the prognostic factors associated with CAD in COPD and investigate the independent risk factors for mortality in COPD patients who underwent comprehensive cardiac evaluations

II. SUBJECTS AND METHODS

We retrospectively reviewed 5207 patients with airway disease who on an outpatient basis visited pulmonology clinic and cardiology clinic in Ajou University Hospital (a university affiliated 1,000-bed sized tertiary referral center in Suwon, Republic of Korea) from Jan 2000 to Dec 2012. Among them, we enlisted 405 patients with COPD (male 88.4%, mean age 68.9 ± 9.4 years) who had undergone coronary multi-detector computed tomography or coronary angiography. Based on the interpretation of chest radiographs by radiologists, 29 patients with physician diagnosed asthma, 8 patients with lung cancer, 27 patients with tuberculous destroyed lung, 5 patients with severe bronchiectasis, and 2 patients with pneumoconiosis were excluded from our study as in figure 1.

Absence of coronary artery disease was proven in 74 patients by coronary multi-detector computed tomography without coronary angiography and coronary angiography was performed by cardiologists in 331 patients. Clinical history, co-morbidities, demographics, medication history, laboratory findings, and radiological findings were acquired by reviewing medical records. Clinical and laboratory parameters were obtained at the time of cardiac evaluation. Survival period was calculated from the time of cardiac evaluation. Mean observation period was 5.5 ± 4.0 years. Survival status was obtained from telephone interview, medical records, or Statistics Korea (kostat.go.kr).

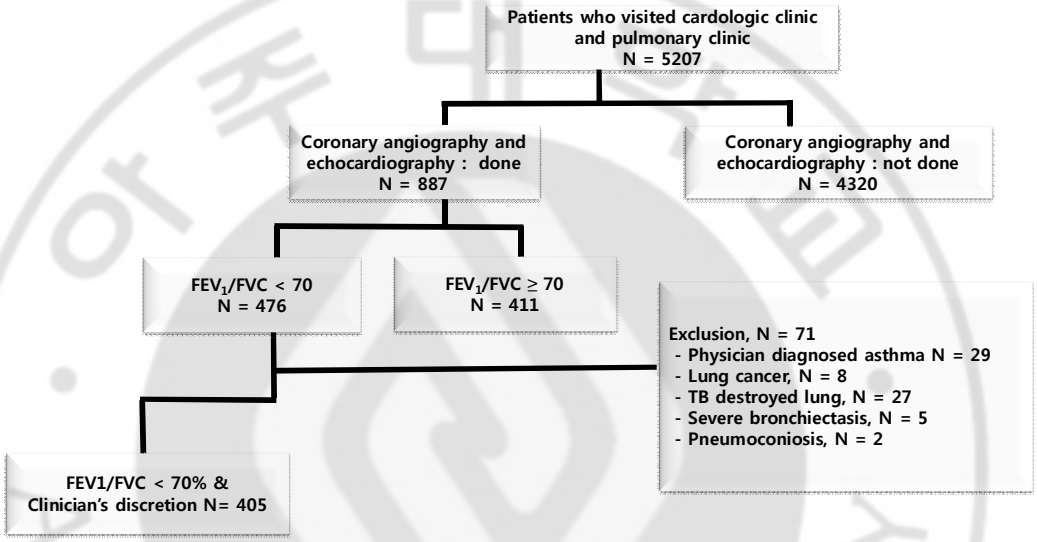

Fig. 1. Flow diagram of subjects.

A. Definitions

The diagnosis of COPD was determined by clinician's judgement and previously documented airflow limitation (forced expiratory volume in 1 second [FEV_1]/ forced vital capacity [FVC] <70% that was not fully reversible) [1]. No or minimal abnormality on chest radiography. CAD was defined as more than 50% stenosis of at least one major epicardial coronary artery. The presence or absence of CAD was confirmed by cardiologists. Left heart failure was defined as ≤40% ejection fraction according to echocardiographic findings reported by cardiologists [20]. Data on duration and amount of cigarette smoking was obtained and an ex-smoker was defined as a subject who had not smoked for at least 1 year. Body mass index (BMI) was calculated as the body weight divided by the height squared (kg/m^2). Acute exacerbation was defined according to the GOLD document [1]. If the patient's condition worsened and a course of oral corticosteroid and antibiotics was indicated based on

the clinician's judgment, exacerbation was defined as moderate. If hospitalization was required at the discretion of the clinician, exacerbation was considered severe. We included only moderate and severe exacerbations in the exacerbation group of COPD as in other studies [21-22]. Spirometry (Elite-DX or CPFS; Medgraphics, MN, USA) was performed according to the American Thoracic Society guidelines [23].

B.Statistical analysis

SPSS version 12 (SPSS Inc., Chicago, IL, USA) was used for the analysis. All values were expressed as means ± standard deviation. The Chi-Square test and/or Fisher's exact test were used for categorical data. The student T-test was used for continuous data. We constructed the 95% confidence interval (CI) of each variable. Simple and multiple logistic regression analyses of significant variables from previous analyses were performed. Clinically significant variables that showed statistically significant odds ratios from simple logistic regression models were selected for inclusion in multiple forward stepwise logistic regression models. Irrespective of the results of univariate analysis, age, gender, and smoking status were included in multiple logistic regression analysis. Survival curves were plotted using the Kaplan–Meier method, and the significance of differences between groups was analyzed using the log-ranks test. A Cox proportional hazards model was used for multivariate analysis to evaluate factors contributing to survival. A *p*-value less than 0.05 was deemed to indicate statistical significance.

C. Ethics Statement

The present study was approved by the Institutional Review Board of Ajou University Hospital.

III. RESULTS

A. Baseline characteristics between COPD with CAD and COPD without CAD

COPD with CAD group was older and male predominant compared to COPD without CAD ($p<0.05$), although baseline pulmonary functions such as FEV_1, $FEF_{25-75\%}$, and FVC after bronchodilator challenge were better in COPD with CAD than COPD without CAD. However, there was no significant difference in smoking history and BMI. COPD patients with CAD used aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and β-blockers more often than COPD patients without CAD ($p<0.05$) (Table 1).

Table 1. Baseline characteristics of COPD with CAD and without CAD

	COPD with CAD	COPD without CAD	*p*-value
Total number	209	196	
Age (years)	70.1 ± 9.7	67.7 ± 8.9	0.009
Gender (Male)	92.3%	84.2%	0.013
Smoking % (Sm: Ex: Never)	47.3 : 40.6 : 12.1 %	44.3 :38.1 : 17.5%	0.218
Smoking (pack year)	45.5 ± 24.4	42.5 ± 24.7	0.262
BMI (kg/m^2)	23.3 ± 3.4	23.2 ± 3.5	0.637
Pulmonary function (% predicted)			
Before bronchodilator challenge			
FVC (%)	84.2 ±21.4	81.2 ± 18.3	0.137
FEV_1 (%)	62.4 ±18.9	57.7 ± 18.3	0.011
FEV_1/FVC (%)	54.8 ±10.9	53.6 ± 12.8	0.312
FEF_{25-75} (%)	34.6 ± 17.2	31.2 ± 15.7	0.038
D_{LCO} (%)	56.3 ± 19.5 [62]	56.4 ± 17.0 [50]	0.929
After bronchodilator challenge			
FVC (%)	89.6 ± 19.5[62]	85.3 ± 17.3[62]	0.052
FEV_1 (%)	66.5 ± 18.3[62]	61.7 ± 18.5[62]	0.028
FEV_1/FVC (%)	55.5 ± 10.5[62]	54.3 ± 11.7[62]	0.373
FEF_{25-75} (%)	40.1 ± 17.9[62]	39.0 ± 18.2[62]	0.623
Medication			
Inhaler corticosteroid	48.3% [101/209]	55.1% [108/196]	0.173
LAMA	51.2% [107/209]	52.0% [102/196]	0.865
Theophylline	53.6% [112/209]	60.7% [119/196]	0.148
Aspirin	91.4% [191/209]	48.0% [94/196]	< 0.001
β-Blocker	33.5% [70/209]	9.2% [18/196]	< 0.001
ACE inhibitor	23.0% [48/209]	13.8% [27/196]	0.017

ACE inhibitor = converting enzyme inhibitor, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease, DLCO = diffusion capacity of carbon monoxide, FEV_1 = forced expiratory volume in 1 second, $FEF_{25-75\%}$ = forced expiratory flow 25–75%, FVC = forced vital capacity, LAMA= long-acting muscarinic antagonist. Continuous variables are presented as means ± standard deviation. Categorical variables are expressed as numbers of subjects or percentages in parentheses. The number of participants is noted in square brackets, if any values for

each item were missing.

B. Comparison of laboratory findings and comorbidities between COPD with CAD and COPD without CAD (Table 2).

Hemoglobin level and serum HDL were lower in COPD with CAD than in COPD without CAD (p<0.05). Diabetes, hypertension, left heart failure, and/or cerebral stroke were combined more frequently in COPD with CAD, compared to COPD without CAD (p<0.05). However, no significant difference was found in the rate of acute exacerbation after enrollment between two groups.

Table 2. Comparison of laboratory findings and co-morbities between COPD with CAD and without CAD.

	COPD with CAD	COPD without CAD	*p*-value
Total number	209	196	
Complete blood count			
WBC ($\times 10^3/\mu L$)	8.4 ± 4.0	7.9 ± 2.8	0.192
Hemoglobin (g/dL)	12.9 ± 1.9	13.4 ± 2.0	0.012
Platelet ($\times 10^3/\mu L$)	233.9 ± 67.8	240 ± 72.2	0.356
Fibrinogen (mg/dL)	410.9 ± 116.3 [63]	456.1 ± 154.0 [48]	0.060
Total cholesterol (mg/dL)	166.2 ± 38.8	163.7 ± 38.4	0.526
LDL cholesterol (mg/dL)	92.7 ± 34.6	95.8 ± 35.0	0.704
HDL cholesterol (mg/dL)	43.7 ± 12.7	48.6 ± 15.3	0.002
Co-morbities			
Diabetes mellitus	24.9% [52/209]	15.9% [31/195]	0.026
Hypertension	63.6% [133/209]	47.2% [92/195]	0.001
Left heart failure	25.0% [50/200]	13.2% [23/174]	0.004
Cerebral stroke	6.3% [13/206]	2.1% [4/193]	0.036
Acute exacerbation per year	0.45 ± 0.80 [189]	0.65 ± 1.28[175]	0.068

CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, WBC = white blood cell. Continuous variables are presented as the mean ± standard deviation. Categorical variables are expressed as percentages or numbers of subjects in square brackets .The number of participants is noted in square brackets, if there are missing data for each item.

C. Prognostic factors of CAD in COPD

Using simple logistic regression analysis, presence of CAD was associated with older age (OR=1.029), male gender (OR=2.266), diabetes (OR=1.752), hypertension (OR=1.959), cerebral stroke (OR=3.185), left heart failure (OR=2.188), lower HDL level (OR=0.975), and lower serum hemoglobin level (OR=0.876) (p<0.05) (Table 3). Multiple logistic regression analysis of risk factors significant by simple logistic analysis was performed to detect independent predictors. Male gender (OR=2.273), hypertension (OR=1.763), left heart failure (OR=2.096), lower HDL level (OR=0.981), and lower hemoglobin level (OR=0.842) were independently associated with the presence of CAD in total COPD group (p<0.05) (Table 4).

Table 3 Predictors of coronary artery disease in the patients with COPD by Multi-variate forward stepwise logistic regression analysis

	Bi-variate model		Multi-variate model	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (years)	1.029(1.007-1.051)	0.010		
Male	2.266(1.197-4.290)	0.012	2.273(1.022-5.051)	0.044
Smoker	1.244(0.370-1.130)	0.126		
BMI (kg/m^2)	1.014(0.958-1.073)	0.637		
Co-morbidities				
Diabetes Mellitus	1.752(1.067-2.876)	0.027		
Hypertension	1.959(1.316-2.917)	0.001	1.764(1.064-2.925)	0.028
Left heart failure	2.188(1.271-3.767)	0.005	2.096(1.070-4.106)	0.031
Cerebral Stroke	3.185(1.019-9.901)	0.046		
Laboratory findings				
HDL cholesterol (mg/dL)	0.975(0.959-0.991)	0.003	0.981(0.964-0.999)	0.041
WBC (x10^3/μL)	1.042(0.979-1.108)	0.198		
Hemoglobin (g/dL)	0.876(0.789-0.972)	0.013	0.842(0.732-0.969)	0.016
Acute exacerbation(rate/year)	1.003(0.579-1.736)	0.993		
FEV_1 %	1.014(1.003-1.025)	0.012		

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, HDL = high-density lipoprotein, WBC = white blood cell. Values in parentheses below the means are 95% confidence intervals. All variables were

analyzed using simple and multiple logistic regression models.

Table 4. Prognostic Factors for the Mortality in total COPD group by Univariate Cox Model.

	N	Hazard Ratio	95%CI	***p*-value**
Age (years)	405	1.050	1.030 – 1.070	<0.001
Gender (male)	405	1.141	0.780 – 2.564	0.254
Smoking (Sm:Non-Sm)	401	1.216	0.934 – 1.584	0.147
BMI (kg/m^2)	405	0.862	0.815 – 0.913	<0.001
Ejection fraction (%)	374	0.972	0.961 – 0.983	<0.001
Co-mobidities				
Coronary artery disease	405	1.365	0.957 – 1.947	0.086
Triple vessel disease vs. no CAD	260	1.193	1.109 – 1.396	0.028
Left heart failure	374	2.106	1.434 – 3.092	<0.001
Hypertension	404	1.211	0.849 – 1.727	0.290
Cerebral stroke	399	1.411	0.575 – 3.465	0.453
Diabetes mellitus	404	1.413	0.949 – 2.103	0.089
Exacerbation (rate/year)	364	1.073	0.935 – 1.230	0.318
Pulmonary function test				
FVC (%)	405	0.986	0.977 – 0.994	0.001
FEV_1 (%)	405	0.977	0.968 – 0.987	<0.001
D_{LCO} (%)	112	0.974	0.952 – 0.998	0.031
FEV_1 (%) after bronchodilator	283	0.975	0.962 – 0.988	<0.001
Labaratory findings				
WBC ($x10^3/\mu L$)	388	1.001	0.954 – 1.050	0.966
Hemoglobin (g/dL)	388	0.781	0.722 – 0.846	<0.001
Plalet ($x10^3/\mu L$)	388	1.000	0.997 – 1.002	0.797
Serum creatinine (mg/dL)	391	1.214	1.070 – 1.379	0.003
Total cholesterol (mg/dL)	391	0.997	0.992 – 1.001	0.188
Serum HDL (mg/dL)	318	1.005	0.992 – 1.019	0.436
Serum protein (g/dl)	388	0.668	0.551 – 0.811	<0.001
Serum albumin (g/dl)	388	0.404	0.294 – 0.555	<0.001

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, Ejection fraction (%) = left ventricular ejection fraction, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, WBC = white blood cell

D.Survival analysis

Among the 126 patients with COPD who died during the observation period, mortality was most frequently due to ischemic heart disease (27 patients, 21.4%). Other causes were respiratory failure including acute exacerbation of COPD (25 patients), cancers other than lung cancer (19 patients), lung cancer (11 patients), pneumonia (8 patients), cerebrovascular disease (6 patients), septic shock (4 patient), pulmonary embolism (1 patient) and unknown causes (1 patient), etc (24 patients). Only all-cause mortality was used for survival analysis, because the cause of death was not detected some cases of non-survivors. According to the univariate cox model, age, BMI, left heart failure, serum hemoglobin level, FVC, FEV_1, D_{LCO}, serum creatinine level, serum protein level, and serum albumin level were significant parameters of all-cause mortality (Table 6). Multivariate analysis by the Cox regression model showed that older age (HR 1.027 per one year, 95% CI 1.005 – 1.049, $p = 0.017$), lower BMI (HR 0.922 per one kg/m^2, 95% CI 0.869 – 0.978, $p = 0.007$), lower left ventricular ejection fraction (HR 0.984 per one percent, 95% CI 0.972 – 0.996, $p = 0.007$), FEV_1 (HR 0.982 per 1% increase of FEV_1, 95% CI 0.972 – 0.991, $p = 0.001$), and lower hemoglobin level (HR 0.843 per 1 g/dl, 95% CI 0.771 – 0.922, $p < 0.001$) were independent risk factors for higher mortality in total COPD patients (Table 5).

Table 5. Prognostic Factors for the Mortality in Total COPD Group by Multivariate Cox Regression Analysis

	Hazard Ratio	95%CI	*p*-value
Age (year)	1.027	1.005 – 1.049	0.017
BMI (kg/m^2)	0.922	0.869 – 0.978	0.007
Ejection fraction (%)	0.984	0.972 – 0.996	0.007
FEV_1 (%)	0.982	0.972 – 0.991	<0.001
Hemoglobin (g/dL)	0.843	0.771 – 0.922	<0.001

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ejection fraction = left ventricular ejection fraction, FEV_1 = forced expiratory volume in 1 second

In Kaplan –Meier survival analysis, COPD without CAD group (mean survival = 12.75 ± 0.68 years) has a tendency to survive longer than COPD with CAD group (mean survival = 9.92 ± 0.53 years, $p = 0.084$), though this parameter was not significant in multivariate analysis by the Cox regression model (Figure 2). COPD with CAD of triple vessel disease group (mean survival = 8.8 ±

0.90 years) had a shorter survival period, compared to the control group (mean survival = 12.75 ± 0.68 years) (p = 0.028) (Figure 2). In keeping with multivariate analysis, COPD without left heart failure (mean survival = 12.26 ± 0.58 years) survived longer than COPD with left heart failure (mean survival = 7.26 ± 0.72 years) (p < 0.001) (Figure 2).

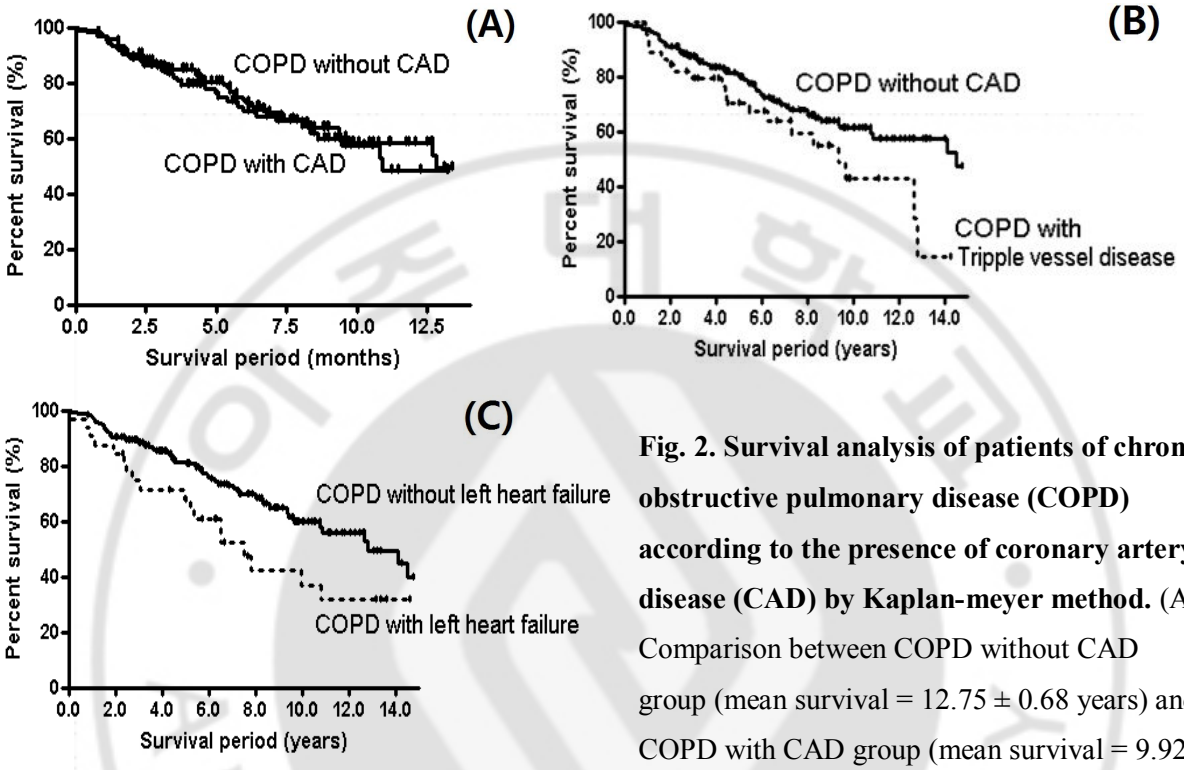

Fig. 2. Survival analysis of patients of chronic obstructive pulmonary disease (COPD) according to the presence of coronary artery disease (CAD) by Kaplan-meyer method. (A) Comparison between COPD without CAD group (mean survival = 12.75 ± 0.68 years) and COPD with CAD group (mean survival = 9.92 ± 0.53 years) (p = 0.084). (B) Comparison between COPD without CAD group (mean survival = 12.75 ± 0.68 years) and COPD with CAD of triple vessel disease group (mean survival = 8.8 ± 0.90 years) (p = 0.026). (C) Comparison between COPD without left heart failure (mean survival = 12.26 ± 0.58 years) and COPD with left heart failure (mean survival = 7.26 ± 0.72 years) (p < 0.001).

IV. Discussion

The aim of this study was to investigate the effect of cardiovascular comorbidities on the prognosis of COPD, and to identify the prognostic factors associated with the CAD in COPD. Our study demonstrated that older age, lower BMI, worse left ventricular ejection fraction, lower FEV_1, and lower hemoglobin level were independent risk factors for the mortality of COPD patients. Male gender, hypertension, left heart failure, and lower serum HDL level were independent predictors for

the presence of CAD in COPD. According to the Towards a Revolution in COPD Health (TORCH) trial, 27% of deaths that occurred during the observation period were due to cardiovascular causes [5]. One study reported that mortality for patients with COPD who had CAD reached 21 % at the 3 year follow up in a study of 4528 patients [24]. However, the true impact of CAD on the survival of COPD was not well explained because of the possibility of occult CAD in COPD which should be confirmed by coronary angiography was not identified in most studies [24-25]. Occult CAD is reported to be found in 59% of COPD patients and even severe CAD was detected in 15% of COPD group [16]. We are of the opinion that our study could verify the influence of CAD on the prognosis of COPD better than other studies because occult CAD was not included in the negative control which was confirmed by angiography carried out by cardiologists. The prevalence of CAD in COPD ranges from 4.7% to 60% [3, 19, 26]. However, our study could not precisely measure the true prevalence of CAD in COPD because only COPD patients who visited the cardiology clinic for evaluating CAD were enrolled.

We herein reported some noteworthy findings. Firstly, our study found that lower left ventricular ejection fraction and lower hemoglobin level were prognostic factors independently associated with the higher mortality of COPD, in addition to well known factors such as FEV_1, age, and BMI, whereas the presence of CAD was not. Interestingly, our data revealed that though COPD with CAD survived shorter than COPD without CAD, not the CAD presence but low left ventricular ejection fraction was proved to be an independent risk factor for the survival of patients with COPD in multivariate Cox analysis, regardless of airway obstruction. However, further studies with bigger cohort are required as to how the CAD of muti-vessel disease would influence the survival of COPD because our data showed the survival of CAD of triple vessel disease group had a shorter survival period, though not proven in multivariate analysis.

There are limited data yet suggesting that decreased left heart function marked by lower ejection fraction is independently associated with the mortality of COPD, regardless of airflow limitation. Recent report only suggested that in mechanically ventilated patients with severe exacerbation of COPD, unrecognized left ventricular failure is common and the early detection and appropriate treatment of left ventricular failure improves long-term quality of life, morbidity, and mortality [27]. Currently, it was reported that left ventricular ejection fraction was not associated with percent emphysema and airflow obstruction, although COPD and reduced FEV_1 are markers for cardiovascular mortality [15, 24, 28]. However, our survival data cannot be generalized until they are validated by future studies, because our cohort cannot represent general population of COPD, considering that out cohort enrolled COPD patients who visited cardiology clinic. Secondly, male gender, lower HDL level, lower hemoglobin level, hypertension, and left heart failure were independently associated with the presence of CAD in COPD. Defining prognostic factors associated

with the presence of CAD in COPD has been required for better management of patients with COPD. Our data revealed that hypertension and left heart failure as well as lower HDL level and lower hemoglobin level were independently factors associated with CAD in COPD. These findings suggest that multidisciplinary approaches are required in the care of COPD patients with CAD.

Our findings are supported by the recent evidence that low grade systemic inflammation is associated with an increased risk of major co-morbidities in COPD independent of smoking, because anemia is manifested as one of the co-morbidities due to chronic inflammation in COPD [29-30]. Furthermore, CAD in COPD is closely linked with low grade systemic inflammation, because low grade inflammation can lead to atherosclerosis which is the primary cause of CAD [25, 31]. Our data suggested that even in the COPD cohort, low HDL level should alert clinicians to medical intervention for prevention of possible CAD related to atherosclerosis. Significant association between HDL-C and the risk of CAD has been reported by other studies even when pharmacological intervention reduced LDL-C level in the general population [32-33]. However, we were unable to evaluate how the management of prognostic factors found in our study influence the clinical course of COPD because of the retrospective study design. Future investigation by a prospective design appears necessary to verify how modification of each risk factor for the presence of CAD, will affect the prognosis of COPD.

We acknowledge several limitations to the current study. Firstly, since the cohort of this present study was enrolled in single center where evaluation for CAD was performed, selection bias could be present. Secondly, diagnosis of COPD was made by pre-bronchodilator FEV_1 and based on the clinician's judgment because post-bronchodilator test data were not obtained in 30.2% of our cohort. Thirdly, clinical assessments by COPD assessment test (CAT) score, Medical Research Council Dyspnea Scale (MRC score), and St. George Respiratory Questionnaire (SGRQ) were not obtained at the point of initial enrollment because of retrospective design of this study. Fourthly, COPD with CAD did not match COPD without CAD equally, in terms of FEV_1 and gender.

V. CONCLUSION

Our study identified lower left ventricular ejection fraction and lower hemoglobin level along with older age, lower BMI, and lower FEV_1 as independent risk factors for the mortality of COPD patients. Our data suggest that multidisciplinary approaches are required in the care of CAD in COPD patients because male gender, hypertension, left heart failure, and lower serum HDL level were independent predictors for the presence of CAD in COPD.

REFERENCES

(1) Standard journal

1. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187(4):347-65.

2. Han MK, Agusti A, Calverley PM*, et al.* Chronic obstructive pulmonary disease phenotypes: the Future of COPD. *Am J Respir Crit Care Med* 2010; 182: 598-604.

3. Vanfleteren LE, Spruit MA, Groenen M*, et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 728-735.

4. McAllister DA, Maclay JD, Mills NL*, et al.* Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 1208-1214.

5. Calverley PM, Anderson JA, Celli B*, et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-789.

6. Preiss D, Thomas LE, Sun JL*, et al.* Predictors of cardiovascular events in a contemporary population with impaired glucose tolerance: an observational analysis of the Nateglinide and Valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) trial. *BMJ Open* 2012;2.

7. Kameda K, Matsunaga T, Abe N*, et al.* Correlation of oxidative stress with activity of matrix metalloproteinase in patients with coronary artery disease. Possible role for left ventricular remodelling. *Eur Heart J* 2003; 24: 2180-2185.

8. Griendling KK, Ushio-Fukai M. Redox control of vascular smooth muscle proliferation. *J Lab Clin Med* 1998; 132: 9-15.

9. Drager LF, Yao Q, Hernandez KL*, et al.* Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4. *Am J Respir Crit Care Med* 2013; 188: 240-248.

10. Savransky V, Nanayakkara A, Li J*, et al.* Chronic intermittent hypoxia induces atherosclerosis. *Am J Respir Crit Care Med* 2007; 175: 1290-1297.

11. Baraldo S, Bazzan E, Zanin ME*, et al.* Matrix metalloproteinase-2 protein in lung periphery is related to COPD progression. *Chest* 2007; 132: 1733-1740.

12. Yasmin, McEniery CM, Wallace S*, et al.* Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; 25: 372.

13. Vestbo J, Edwards LD, Scanlon PD*, et al.* Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365: 1184-1192.

14. Barr RG, Ahmed FS, Carr JJ*, et al.* Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA Lung Study. *Eur Respir J* 2012; 39: 846-854.

15. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005; 127: 1952-1959.

16. Reed RM, Eberlein M, Girgis RE*, et al.* Coronary artery disease is under-diagnosed and under-treated in advanced lung disease. *Am J Med* 2012; 125: 1228 e13-1228 e22.

17. Brekke PH, Omland T, Smith P*, et al.* Underdiagnosis of myocardial infarction in COPD - Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med* 2008; 102: 1243-1247.

18. Williams MC, Murchison JT, Edwards LD*, et al.* Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality. *Thorax* 2014.

19. Sidney S, Sorel M, Quesenberry CP, Jr.*, et al.* COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068-2075.

20. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA et al. Heart Fialure Society of America 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* 2010 Jun;16(6):e1-194

21. Wouters EF, Postma DS, Fokkens B*, et al.* Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005; 60: 480-487.

22. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786-796.

23. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107-1136.

24. Berger JS, Sanborn TA, Sherman W*, et al.* Effect of chronic obstructive pulmonary disease on survival of patients with coronary heart disease having percutaneous coronary intervention. *Am J Cardiol* 2004; 94: 649-651.

25. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; 107: 1514-1519.

26. Mullerova H, Agusti A, Erqou S*, et al.* Cardiovascular comorbidity in COPD: systematic literature review. *Chest* 2013; 144: 1163-1178.

27. Matamis D, Tsagourias M, Papathanasiou A et al. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. J Crit Care. 2014 Apr;29(2):315.e7-14. 26.

28. Barr RG1, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010 Jan 21;362(3):217-27.

29.Agusti A, Edwards LD, Rennard SI*, et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.

30.Thomsen M, Dahl M, Lange P*, et al.* Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 982-988.

31.Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999; 340: 115-126.

32.Schaffer A, Verdoia M, Barbieri L*, et al.* High-Density Lipoproteins and Coronary Artery Disease:

A Single-Center Cohort Study. *Angiology* 2013.

33. Acharjee S, Boden WE, Hartigan PM, *et al.* Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: A post-hoc analysis from the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). *J Am Coll Cardiol* 2013; 62: 1826-1833.

– 국문요약 –

관상동맥질환을 동반한 만성폐쇄성폐질환 환자의 임상적 특징에 대한 연구

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배경 : 관상동맥질환은 만성폐쇄성폐질환 환자에게서 흔히 동반되는 질환이며, 심혈관계사망은 만성폐쇄성폐질환 환자의 주요 사망원인 중 하나로 알려져 있다. 따라서 만성폐쇄성폐질환 환자에게서 관상동맥질환과 연관된 예후 인자를 찾고, 만성폐쇄성폐질환 환자의 사망에 영향을 미치는 독립인자들을 규명하고자 본 연구를 시행하였다.

방법 : 2000년 1월부터 2012년 12월까지 아주대병원 호흡기내과에 방문하여, 폐기능검사를 통해 만성폐쇄성폐질환이 확정된 환자 중, 관상동맥 CT검사와 관상동맥 조영술을 통해 관상동맥질환의 유무가 확인된 405명의 환자를 대상으로, 관상동맥질환을 동반한 군과 동반하지 않은 군으로 나누어 후향적 연구를 진행하였다.

결과 : 남성, 고혈압, 좌심실부전, 낮은 헤모글로빈 수치와 HDL 수치가 만성폐쇄성폐질환 환자의 관상동맥질환 동반여부와 관련이 있는 독립인자들로 확인되었다($p<0.05$). 고령, 낮은 BMI 수치, 낮은 좌심실 박출계수, 낮은 FEV1, 낮은 헤모글로빈 수치가 만성폐쇄성폐질환 환자의 높은 사망률과 관련된 독립인자들이다($p<0.05$).

결론 : 본 연구에서 고령, 낮은 BMI 수치, 낮은 좌심실 박출계수, 낮은 FEV1, 낮은 헤모글로빈 수치가 만성폐쇄성폐질환 환자의 높은 사망률과 관련된 독립인자들이었고, 남성, 고혈압, 좌심실부전, 낮은 헤모글로빈 수치, 낮은 HDL 수치가 만성폐쇄성폐질환 환자의 관상동맥질환 동반과 관련된 독립인자들이었다. 따라서 관상동맥질환을 동반한 만성폐쇄성폐질환 환자를 치료할 때 여러 동반 질환에 대한 관리가 필요한 것으로 사료된다.

핵심어 : 만성폐쇄성폐질환, 관상동맥질환, 사망률