Prognostic factors in patients with chronic obstructive pulmonary disease

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Prognostic factors in patients with chronic obstructive pulmonary disease

Directed by Professor Young Sam Kim

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ABSTRACT

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Backgrounds: Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airway obstruction that is partially reversible. It is a major cause of chronic morbidity and mortality in the world. However, the accurate mortality of COPD or the prognostic factors in Korean are not well known. The purpose of this study is to analyze the factors related to COPD prognosis using large population-based database.

Methods: We used a health screening cohort including sampled 514,866 populations. It was consisted of insurance eligibility, medical treatment, general health examinations, and medical care institutions information. COPD patients more than 40 years old were selected from 2002 to 2013, and divided into survivors and non-survivors. A Cox proportional hazards model was used to identify independent variables for mortality of COPD.

Results: A total of 21,622 COPD patients were included, and survivors were 16,757 and non-survivors were 4,865. The mean age of COPD patients was 67.2, and men were 63.5%. Elderly patients with comorbidities were more likely to be non-survivors. Medical utilization including hospitalization,

emergency room visit, intensive care unit admission, and COPD medications use were also more frequent in non-survivor group. Smoking, underweight, and anemia were associated with non-survivors. In multivariate analysis, the non-survivors had the features including male gender (the hazard ratio [HR] of female 0.48, 95% confidence interval [CI] 0.42-0.55), older age (HR of 50-59 years 2.91, 95% CI 1.63-5.19; HR of 60-69 years 5.54, 95% CI 3.18-9.66; HR of 70-79 years 12.05, 95% CI 6.93-20.95; HR of ≥ 80 years 20.29, 95% CI 11.51-35.77), living in non-metropolitan area (HR 1.16, 95% CI 1.04-1.29), more comorbidities (HR of hypertension 1.14, 95% CI 1.02-1.27; HR of congestive heart failure 1.39, 95% CI 1.12-1.71; HR of diabetes mellitus 1.27, 95% CI 1.11-1.46; HR of tuberculosis 1.34, 95% CI 1.10-1.63), more healthcare use (HR of hospitalization 1.35, 95% CI 1.19-1.54; HR of intensive care unit admissions 1.80, 95% CI 1.56-2.09), current smoking (HR 1.18, 95% CI 1.06-1.32), underweight (HR 1.67, 95% CI 1.47-1.91), and lower hemoglobin (HR of normocythemic 0.71, 95% CI 0.64-0.79).

Conclusions: This study has showed a number of prognostic factors associated with COPD mortality. These clinical parameters may be useful to predict high risk COPD patients for poor prognosis. We also may achieve optimal management for COPD through the treatment of modifiable risk factors.

Key words: COPD, mortality, prognostic factors, comorbidity, medical use, health screening

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I. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common disease and prevalence is increasing in worldwide. It is characterized by persistent airway obstruction that is partially reversible. COPD is a major cause of chronic morbidity and mortality in the world[1]. The prevalence and burden of COPD are increasing because people live longer and have more exposure to risk factors. Estimate of prevalence and incidence of COPD is different according to the study population and diagnostic criteria[1,2]. Meta-analysis of 62 studies published between 1990 and 2004 that included prevalence estimates from 28 different countries, reported a pooled prevalence of COPD of 7.6%[3]. In South Korea, nationwide epidemiologic survey called Korean National Health and Nutrition Examination Survey III (KNHANES III) was performed in 2001. The prevalence of airflow limitation was 17.2% (men, 25.8%; women, 9.6%) among adults older than 45 years. Most of these cases were mild in degree, and only a minority of these subjects had received physician diagnosis or treatment[4].

COPD is one of the most important causes of death worldwide. The Global Burden of Disease Study estimated that COPD will become the fourth leading cause of death worldwide in 2030[5]. By the annual report on the causes of death statistics in Korea, chronic lower airway disease is the seventh leading cause of death in 2014[6]. The total number of deaths is 7,717 with a death rate of 14.1 per 100,000 populations. However, it is difficult to consider the report of Statistics Korea as the accurate mortality of COPD because it is an underdiagnosed and undertreated disease[7,8].

Mortality in patients with COPD is related to various measures including forced expiratory volume in one second (FEV1), the ratio of inspiratory to total lung capacities, exercise capacity, dyspnea scores, body mass index, and exacerbation frequency[9]. Some treatments can also modify the prognosis of COPD. Smoking is the most important factor related to COPD progression. Smoking cessation is the most effective way to reduce the progression and mortality of COPD[10,11]. Long term oxygen therapy and lung volume reduction surgery can also reduce the mortality in selected patients with advanced disease[12-15]. Other treatment including pharmacologic therapy, respiratory rehabilitation, or treatment for comorbidity has not been conclusively shown to reduce the mortality.

In Korea, there are no studies of the exact mortality of patients with COPD. Although many studies have described COPD mortality, there are no population-based studies on the long-term mortality of COPD in Korea. Therefore, the factors associated with the mortality and burden of COPD are not well known. The purpose of this study is to analyze the factors related to COPD

prognosis using large population-based database.

II. MATERIALS AND METHODS

1. Source of data

Since 2000, the National Health Insurance (NHI) systems in Korea have provided the health insurance service to nearly all people living in Korea. Consequently, a large amount of health-related database has accumulated in the NHI database system. Using this database, the Korean NHI Corporation has established a research database. Because all Koreans have been recommended to have a national health screening every two years, the NHI Corporation was able to make a health screening database. This database comprised a random selection of 10% (n=514,866) of all health screening participants (n=5,150,000) in 2002 and 2003. From 2002 to 2003, a total of 5 million people between the ages of 40 and 79 have received national health screening (Figure 1). Among them, 0.5 million people were sampled and followed up from 2002 to 2013. NHI system provides medical aid services, which is a public assistance system that guarantees medical problems of low-income populations. We excluded the medical aid populations for analysis because the medical aid system was implemented after 2008.

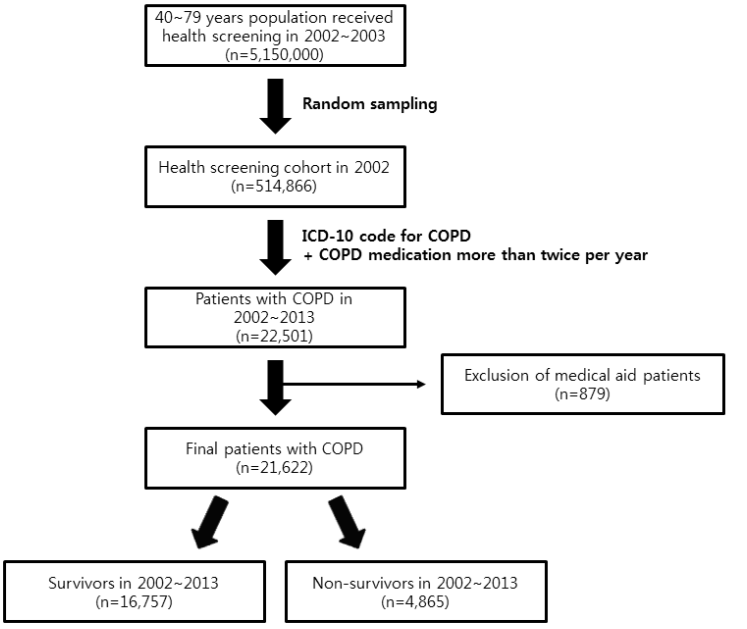

Figure 1. Flow chart of the inclusion and exclusion of populations.

2. Composition of the health screening database

The health screening cohort consisted of insurance eligibility, medical treatment, general health examinations, and medical care institutions database during 12 years (Figure 2). Insurance eligibility database included the information of gender, age, death, residence, income, and disability. Medical treatment database included disease, healthcare use, medical cost, treatment, and medication. General health examinations database included health questionnaire and laboratory data. Medical care institutions database included institutional type, status by area, facilities, personnel, and equipment.

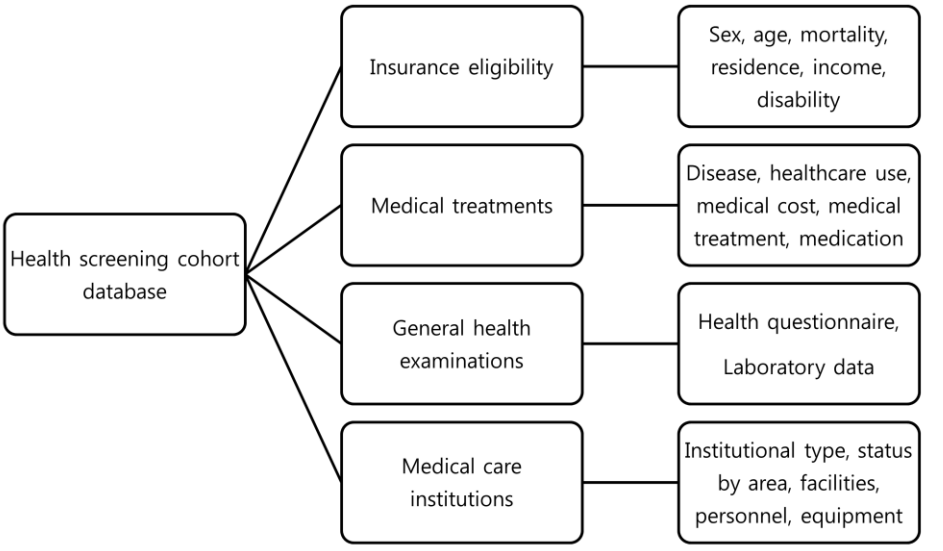

Figure 2. Details of the health screening cohort database.

3. Study population

Because the NHI database did not include a spirometry data essential for the diagnosis of COPD and did not also include an individual's medical history or symptoms, we identified COPD patients using the International Classification of Disease-Tenth Revision (ICD-10) and prescription details in the health screening cohort (Figure 1). We used the diagnostic criteria that an individual should visit the medical facility at least twice per year with both a COPD diagnostic code and a prescription for one or more COPD medications. Similar to previous studies[16-19], COPD patients were identified by having all following

criteria: older than 40 years; ICD-10 codes for COPD (J43-J44, except J430); COPD medication use at least twice per year. COPD medications include long-acting muscarinic antagonist (LAMA), long-acting beta-2 agonist (LABA), inhaled corticosteroid (ICS), ICS plus LABA, short-active muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA), methylxanthines, systemic corticosteroids, and systemic beta agonists.

4. Determinants of disease and demographic factors

Comorbidities included hypertension (I10.x), ischemic heart disease (I20.x–I25.x,except I20.1), congestive heart failure (I50, I50.0, I50.1, I50.9), osteoporosis (M80.x–M82.x), depressive disorder (F32.x–F33.x), arthritis (M05.x–M09.x, M13.x), diabetes mellitus (E10.x–E14.x), gastroesophageal reflux disease (K21, K21.0, K21.9), hyperlipidemia (E78.0, E78.4, E78.5), anemia (D50.x–D53.x, D63.x), metabolic syndrome (E889), bronchiectasis (J47), tuberculosis (A15.x-A19.x). High grade COPD is defined by having following criteria based on a previous study: use of triple inhaler therapy regularly or systemic steroid therapy at least two times per year with COPD inhaler therapy[16].

Health care utilization was analyzed only if they were considered as COPD-related use. Hospitalization, emergency room visit, or intensive care unit (ICU) admission related to COPD was defined to admissions when the primary or secondary diagnosis was COPD or COPD-related disease such as pneumonia (J12-J17), pulmonary thromboembolism (I26), dyspnea (R06), or acute

respiratory distress syndrome (J80), and when COPD-related medication was prescribed.

Smoking status was divided into three groups according to health questionnaire at the first health screening visit. Never-smokers were defined as those who answered that they had not smoked ever. Ex-smokers were defined as those who answered that they had smoked before, but did not smoke at the time of the health screening visit. Current smokers were defined as those who answered that they smoked at the time of health screening visit. Body mass index (BMI) was calculated based on height and body weight. Patients were categorized as underweight (BMI < 18.5), normal (18.5-24.9), obese class I (25-29.9), or obese class II (≥ 30). Blood pressure was categorized as normal (systolic blood pressure < 120 mmHg and diastolic < 80 mmHg), prehypertension (systolic 120-139 mmHg or diastolic 80-89 mmHg), or hypertension (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg). The total cholesterol level was categorized as normal (< 200 mg/dL), elevated (200-239 mg/dL), or severely elevated (≥ 240 mg/dL). Hemoglobin was categorized as anemia (hemoglobin < 12 g/dL in females, < 13 g/dL in males), polycythemia (hemoglobin ≥ 15 g/dL in females, ≥ 17 g/dL in males), or normocythemia.

5. Outcomes

Patients were enrolled at the time of COPD diagnosis and followed up until the end of the study period or death. Survivors were defined as those who were alive during the follow-up period, and non-survivors were defined as who were

died. The time of death consisted of year and month. For cause-specific mortality of COPD, the patients with COPD in 2002 were washed-out and COPD mortality was analyzed from 2003 to 2013. The cause of death was divided into COPD-related (J43-J44), respiratory disease-related (J00-J99), other disease-related except respiratory disease (other codes except J00-J99), and all-cause mortality according to the Korean Standard Classification of Disease and Cause of Death.

6. Statistical analysis

Differences between groups were assessed using the chi-square test for categorical variables and Student's *t*-test for continuous variables. Multivariate logistic regression analysis was performed for all significant covariates in univariate analysis. A Cox proportional hazards model was used to identify independent variables for cause-specific mortality of COPD. Results were presented as hazard ratio (HR) and 95% confidence interval (CI). Violation of proportional hazards assumption was tested by exploring log(-log [survival]) curves. The p value of < 0.05 was considered statistically significant. All statistical analyses were performed with the SAS program, version 9.4 (SAS Institute, Cary, NC, USA).

III. RESULTS

1. Baseline demographics of population of the health screening cohort in 2012.

Total enrolled populations were 514,866, and male was 54.2% and female was 45.8% (Table 1). The most common age group was between 40 and 49 years old. High household income was more frequent than low household income. The region of residence was 44.7% in metropolitan and 55.3% in other areas.

Table 1. Baseline demographics of population of the health screening cohort in 2002

	Total population (n=514,866)
Gender	
Male	279,125 (54.2)
Female	235,741 (45.8)
Age	
40-49 years	236,981 (46.0)
50-59 years	145,032 (28.2)
60-69 years	101,156 (19.6)
≥ 70 years	31,697 (6.2)
Household income	
1st quintile	81,985 (15.9)
2nd quintile	74,069 (14.4)
3rd quintile	81,701 (15.9)
4th quintile	105,777 (20.5)
5th quintile	171,334 (33.3)
Region of residence	
Metropolitan	230,399 (44.7)
Others	284,467 (55.3)

Data are shown as number (percentage).

2. Baseline characteristics of COPD patients

The number of individuals who met the predefined criteria for COPD was 21,622 (Table 2). The proportion of men in COPD patients was higher than the total cohort population. The mean age of COPD patients was 67.2. The age was also higher in patients with COPD than total cohort population. During the study period, 16,757 individuals survived and 4,865 died. Mean follow-up periods were 2,010 days in survivors and 1,293 days in non-survivors. The mortality rate of COPD was 78.7 per 100,000 person-years during the 12-year study period (data not shown). The number of patients with COPD gradually increased from 2,041 in 2002 to 6,144 in 2013 (Figure 3).

Table 2. Baseline demographics of patients with COPD

	Total patients (n=21,622)
Gender	
Male	13,720 (63.5)
Female	7,902 (36.5)
Age	
Mean	67.2±9.3
40-49 years	886 (4.1)
50-59 years	3,565 (16.5)
60-69 years	7,651 (35.4)
70-79 years	7,811 (36.1)
≥80 years	1,709 (7.9)
Survival status	
Survivors	16,757 (77.5)
Non-survivors	4,865 (22.5)
Mean follow-up period (days)	

Survivors	2,009.9 ± 1,278.2
Non-survivors	1,292.6 ± 1,089.1
Total	1,848.5 ± 1,273.9

Data are shown as the mean ± standard deviation or number (percentage).

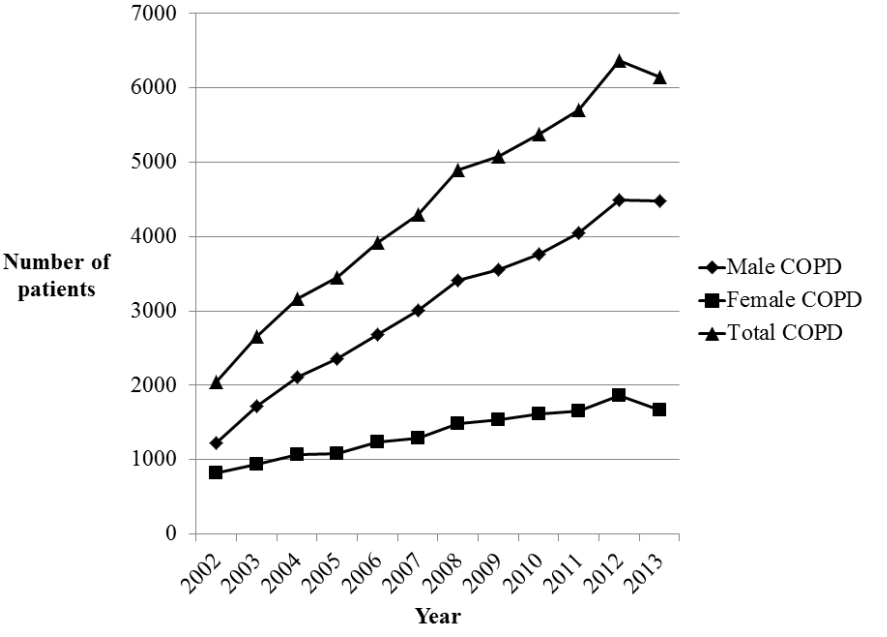

Figure 3. Changes in the number of COPD patients.

3. Baseline characteristics between survivors and non-survivors

Table 3 showed baseline characteristics between survivors and non-survivors. Men were more frequent in non-survivor group, and increased age was also a risk factor for death. Individuals having lower household income showed higher death rate. Individuals living in non-metropolitan area had also more deaths

than metropolitan area. Among the comorbidity, hypertension, congestive heart failure, osteoporosis, diabetes mellitus, gastroesophageal reflux disease, hyperlipidemia, and tuberculosis were more frequent in the non-survivor group. There was no difference between survivors and non-survivors by Charlson comorbidity index or the grade of COPD.

Table 3. Demographic and clinical characteristics of survivors and non-survivors with COPD

	Survivors (n=16,757)	Non-survivors (n=4,865)	P value
Gender			<.0001
Male	9,940 (59.3)	3,780 (77.7)	
Female	6,817 (40.7)	1,085 (22.3)	
Age			<.0001
40-49 years	848 (5.1)	38 (0.8)	
50-59 years	3,292 (19.6)	273 (5.6)	
60-69 years	6,216 (37.1)	1,435 (29.5)	
70-79 years	5,323 (31.8)	2,488 (51.1)	
≥80 years	1,078 (6.4)	631 (13.0)	
Household income			<.0001
1st quintile	2,779 (16.6)	979 (20.1)	
2nd quintile	2,499 (14.9)	853 (17.5)	
3rd quintile	2,896 (17.3)	775 (15.9)	
4th quintile	3,515 (21.0)	947 (19.5)	
5th quintile	5,068 (30.2)	1,311 (26.9)	
Region of residence			<.0001
Metropolitan	5,668 (33.8)	1,350 (27.7)	
Others	11,089 (66.2)	3,515 (72.3)	
Comorbidity			
Hypertension	4,365 (26.0)	1,520 (31.2)	<.0001
Ischemic heart disease	1,090 (6.5)	346 (7.1)	0.1344
Congestive heart failure	481 (2.9)	264 (5.4)	<.0001
Osteoporosis	1,599 (9.5)	306 (6.3)	<.0001

Depressive disorder	843 (5.0)	216 (4.4)	0.0930
Arthritis	2,842 (17.0)	845 (17.4)	0.5022
Diabetes mellitus	1,875 (11.2)	688 (14.1)	<.0001
Gastroesophageal reflux disease	2,214 (13.2)	484 (9.9)	<.0001
Hyperlipidemia	1,699 (10.1)	382 (7.9)	<.0001
Anemia	467 (2.8)	159 (3.3)	0.0782
Bronchiectasis	530 (3.2)	172 (3.5)	0.1970
Tuberculosis	485 (2.9)	288 (5.9)	<.0001
Charlson comorbidity index			0.6749
0-1	272 (1.6)	84 (1.7)	
2	1,027 (6.1)	284 (5.8)	
≥3	15,458 (92.2)	4,497 (92.4)	
Severity			0.1990
Non-high grade	16,243 (96.9)	4,698 (96.6)	
High grade	514 (3.1)	167 (3.4)	

Data are shown as number (percentage).

COPD=chronic pulmonary obstructive disease.

4. Health care utilization and medication use

More health care uses occurred in non-survivor group (Table 4). While only 5,940 (35.5% of total survivors) of survivors have experienced hospitalization, 4,021 (82.7% of total non-survivors) of non-survivors experienced. The emergency room visits and intensive care unit admissions showed a similar tendency. The overall use of COPD drugs occurred more frequent in non-survivors (Table 5). Compared to survivors, the use of ICS, intravenous corticosteroids, SAMA, and SABA were especially frequent in non-survivors. In both groups, oral medications such as systemic beta-2 agonists and methylxanthines were most frequently used among COPD drugs. The number of prescriptions per year was higher in non-survivors. The medication

possession ratio (MPR), which is calculated the sum of the days supplied for all claim during a study period divided by the number of days elapsed during the period, was also higher in non-survivor group.

Table 4. Health care utilization between survivors and non-survivors with COPD

	Survivors (n=16,757)	Non-survivors (n=4,865)	P value
Hospitalization			
History of hospitalizations	5,940 (35.5)	4,021 (82.7)	<.0001
Number of hospitalizations*	1.78±2.47	2.36±2.98	<.0001
Hospitalization period†	19.44±39.99	32.31±50.82	<.0001
ER visits			
History of ER visits	2,137 (12.8)	1,947 (40.0)	<.0001
ER visits*	1.48±1.73	1.76±1.92	<.0001
ICU admission			
History of ICU admissions	625 (3.7)	1290 (26.5)	<.0001
Number of ICU admissions*	2.25±1.96	2.61±2.27	0.0004

Data are shown as the mean ± standard deviation or number (percentage).

*Average number per person who hospitalized, visited to ER, or admitted to ICU.

†Average days per person.

COPD= chronic pulmonary obstructive disease; ER=emergency room; ICU=intensive care unit.

Table 5. Medication use between survivors and non-survivors with COPD

	Survivors (n=16,757)	Non-survivors (n=4,865)	P value
Drug Type			<.0001
ICS	1,567 (9.4)	981 (20.2)	
ICS + LABA	5,021 (30.0)	1,585 (32.6)	
LAMA	4,127 (24.6)	1,339 (27.5)	
LABA	285 (1.7)	11 (0.2)	
IVCS	2,453 (14.6)	1,866 (38.4)	
OCS	7,728 (46.1)	2,682 (55.1)	
SAMA	1,609 (9.6)	1,628 (33.5)	

SABA	4,707 (28.1)	2,430 (49.9)	
SABA+SAMA	378 (2.3)	292 (6.0)	
Systemic beta-2 agonist	8,301 (49.5)	2,754 (56.6)	
Methylxanthine	11,108 (66.3)	3,612 (74.2)	
Number(#) of prescription			<.0001
<1/year	1,629 (9.7)	305 (6.3)	
1≤#≤2/year	8,873 (53.0)	2,243 (46.1)	
3≤#≤4/year	3,896 (23.2)	1,221 (25.1)	
≥5/year	2,859 (17.1)	1,096 (22.5)	
MPR			<.0001
< 20%	12,574 (75.0)	2,295 (47.2)	
20 ~ 39%	1,408 (8.4)	703 (14.5)	
40 ~ 59%	782 (4.7)	398 (8.2)	
60 ~ 79%	511 (3.0)	317 (6.5)	
≥ 80%	1,482 (8.8)	1,152 (23.7)	

Data are shown as number (percentage).

COPD=chronic pulmonary obstructive disease; ICS=inhaled corticosteroids; LAMA=long-acting muscarinic antagonist; LABA=long-acting beta-2 agonist; IVCS=intravenous corticosteroids; OCS=oral corticosteroids; SAMA=short-acting muscarinic antagonist; SABA=short-acting beta-2 agonist; MPR=Medication possession ratio.

5. Health examination findings

Table 6 showed health examination findings between two groups. All measures showed statistically significant differences between groups. While never-smokers were more likely to survive, smokers were more likely to be non-survivors. Underweight was related to higher mortality compared to normal. Higher blood pressure was also related to non-survivors. Anemic individuals were more frequent in non-survivor group.

Table 6. Comparison of smoking status, BMI, blood pressure, laboratory findings between survivors and non-survivors with COPD

	Survivors (n=16,757)	Non-survivors (n=4,865)	P value
Smoking			<.0001
Never-smoker	6,676 (39.8)	1,411 (29.0)	
Ex-smoker	1,844 (11.0)	431 (8.9)	
Current-smoker	2,477 (14.8)	765 (15.7)	
BMI (kg/m^2)			<.0001
<18.5	616 (3.7)	459 (9.4)	
18.5-24.9	6,797 (40.6)	1,761 (36.2)	
25-29.9	3,560 (21.2)	488 (10.0)	
≥30	402 (2.4)	50 (1.0)	
Blood pressure			<.0001
Normal	2,802 (16.7)	608 (12.5)	
Pre-high BP	5,299 (31.6)	1,193 (24.5)	
High BP	3,290 (19.6)	957 (19.7)	
Total cholesterol (mg/dL)			<.0001
<200	6,620 (39.5)	1,762 (36.2)	
200-239	3,396 (20.3)	712 (14.6)	
≥240	1,362 (8.1)	280 (5.8)	
Hemoglobin			<.0001
Anemic	1,694 (10.1)	623 (12.8)	
Normocythemic	9,378 (56.0)	2,065 (42.4)	
Polycythemic	310 (1.8)	67 (1.4)	

Data are shown as number (percentage).

BMI=body mass index; COPD=chronic obstructive pulmonary disease; BP=blood pressure

6. Cause-specific mortality in COPD patients and related factors by Cox proportional hazards models

During the study period, the mean survival time of newly diagnosed COPD patients was 103 ± 0.37 months (data was not shown). Figure 4 showed the annual change in the number of deaths by cause in COPD patients. Respiratory disease-related death accounted for 21.0 % of total COPD death, and COPD-related death accounted for 11.0%. All-cause mortality in COPD patients by cox proportional hazards models was associated with male gender, older age, living in non-metropolitan area, more comorbidities, current smoker, lower BMI, higher blood pressure, lower total cholesterol, lower hemoglobin, and more COPD medications and health care utilization (Table 7, Figure 5-7). The COPD-related mortality was associated with only older age, lower BMI, and more COPD medications and health care utilization (Table 8). The respiratory disease-related mortality was associated with male gender, older age, tuberculosis, lower BMI, and more COPD medications and health care utilization (Table 9). The factors associated with other disease-related mortality except respiratory disease were similar to those associated with all-cause mortality (Table 10).

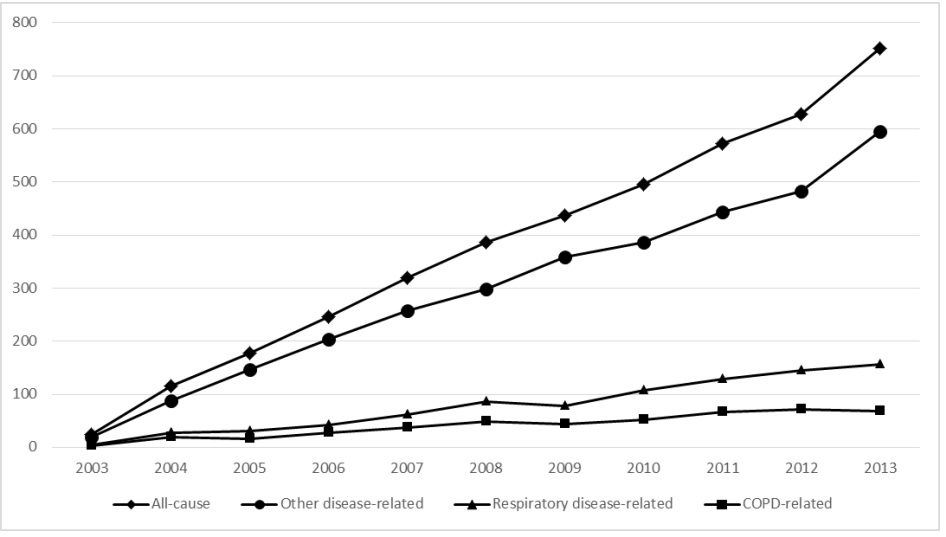

Figure 4. Mortality by cause of death in COPD patients.

Table 7. Cox proportional hazards model for factors associated with all-cause mortality in patients with COPD

	HR	95% CI		P value
Gender				
Male	1.00			
Female	0.48	0.42	0.55	<.0001
Age				
40-49 years	1.00			
50-59 years	2.91	1.63	5.19	0.0003
60-69 years	5.54	3.18	9.66	<.0001
70-79 years	12.05	6.93	20.95	<.0001
≥80 years	20.29	11.51	35.77	<.0001
Household income				
0~20%	1.00			
20~40%	1.04	0.90	1.20	0.6159
40~60%	0.95	0.82	1.11	0.5508
60~80%	0.91	0.79	1.06	0.2149

80~100%	0.88	0.77	1.01	0.0644
Region of residence				
Metropolitan	1.00			
Others	1.16	1.04	1.29	0.0077
Comorbidity				
None	1.00			
Hypertension	1.14	1.02	1.27	0.0184
Congestive heart failure	1.39	1.12	1.71	0.0027
Osteoporosis	1.05	0.85	1.28	0.6693
Diabetes mellitus	1.27	1.11	1.46	0.0007
Gastroesophageal reflux disease	1.02	0.88	1.19	0.8012
Hyperlipidemia	1.03	0.86	1.23	0.7652
Tuberculosis	1.34	1.10	1.63	0.0042
Smoking				
Never-smoker	1.00			
Ex-smoker	0.97	0.85	1.10	0.61
Current-smoker	1.18	1.06	1.32	0.0031
BMI (kg/m^2)				
<18.5	1.67	1.47	1.91	<.0001
18.5-24.9	1.00			
25-29.9	0.79	0.70	0.89	<.0001
≥30	0.93	0.66	1.31	0.6682
Blood pressure				
Normal	1.00			
Pre-high BP	1.00	0.89	1.13	0.9807
High BP	1.08	0.95	1.22	0.2435
Total cholesterol (mg/dL)				
<200	1.00			
200-239	0.89	0.80	0.99	0.0358
≥240	0.99	0.85	1.16	0.911
Hemoglobin				

Anemic	1.00			
Normocythemic	0.71	0.64	0.79	<.0001
Polycythemic	0.64	0.46	0.89	0.0087
Healthcare use				
None	1.00			
Hospitalizations	1.35	1.19	1.54	<.0001
ER visits	1.07	0.94	1.22	0.3137
ICU admissions	1.80	1.56	2.09	<.0001
Medication				
None	1.00			
Oral medication	0.69	0.56	0.85	0.0004
Inhaler + oral medication	0.57	0.47	0.70	<.0001
Number(#) of prescription				
<1/year	1.00			
1≤#≤2/year	1.11	0.93	1.33	0.2622
3≤#≤4/year	0.89	0.72	1.09	0.2533
≥5/year	0.57	0.46	0.72	<.0001
MPR				
< 20%	1.00			
20 ~ 39%	1.76	1.52	2.04	<.0001
40 ~ 59%	1.73	1.44	2.08	<.0001
60 ~ 79%	2.18	1.76	2.69	<.0001
≥ 80%	2.72	2.29	3.23	<.0001

COPD=chronic pulmonary obstructive disease; HR=hazards ratio; CI=confidence interval; BMI=body mass index; BP=blood pressure; ER=emergency room; ICU=intensive care unit; IVCS=intravenous corticosteroids; MPR=Medication possession ratio.

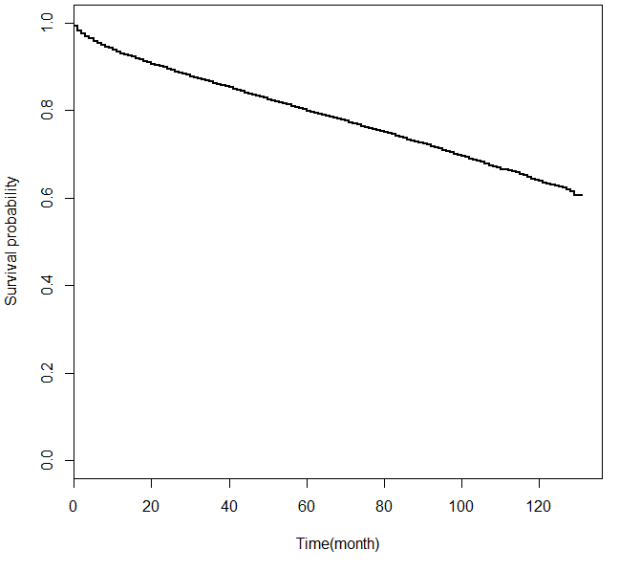

Figure 5. Survival curves of COPD patients.

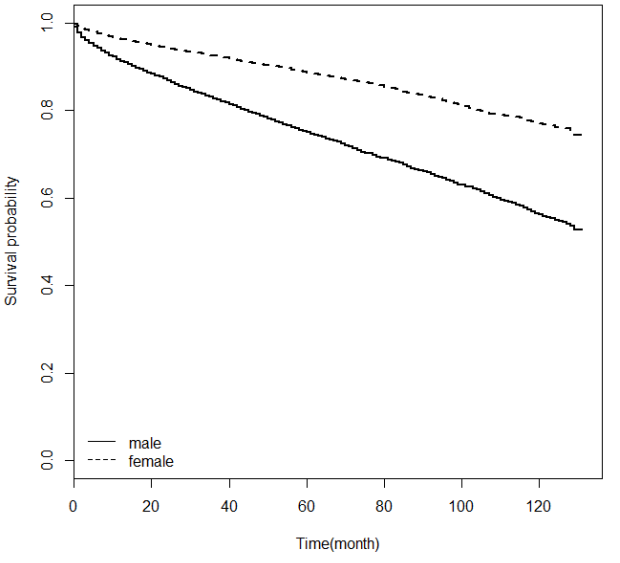

Figure 6. Survival curves of male and female patients with COPD.

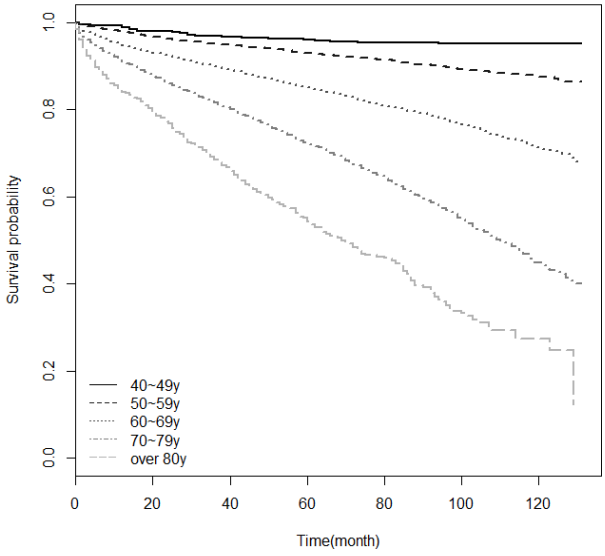

Figure 7. Survival curves according to age of COPD patients.

Table 8. Cox proportional hazards model for factors associated with COPD-related mortality in patients with COPD

	HR		95% CI	P value
Gender				
Male	1.00			
Female	0.89	0.60	1.31	0.541
Age				
40-49 years	NA	NA	NA	NA
50-59 years	1.00			
60-69 years	2.12	1.09	4.14	0.0274
70-79 years	4.34	2.25	8.35	<.0001
≥80 years	6.90	3.25	14.66	<.0001
Household income				

0~20%	1.00			
20~40%	1.19	0.79	1.79	0.4069
40~60%	1.03	0.66	1.61	0.8849
60~80%	1.33	0.89	1.99	0.1663
80~100%	0.85	0.57	1.27	0.4235
Region of residence				
Metropolitan	1.00			
Others	1.01	0.75	1.35	0.971
Comorbidity				
None	1.00			
Hypertension	1.10	0.80	1.52	0.5634
Congestive heart failure	1.05	0.54	2.05	0.8839
Osteoporosis	0.59	0.26	1.37	0.2226
Diabetes mellitus	0.88	0.53	1.44	0.6006
Gastroesophageal reflux disease	1.09	0.68	1.76	0.7153
Hyperlipidemia	0.57	0.26	1.23	0.1504
Tuberculosis	1.08	0.63	1.86	0.7688
Smoking				
Never-smoker	1.00			
Ex-smoker	1.08	0.77	1.51	0.6466
Current-smoker	0.91	0.67	1.25	0.5612
BMI (kg/m^2)				
<18.5	2.67	1.98	3.59	<.0001
18.5-24.9	1.00			
25-29.9	0.59	0.38	0.91	0.018
≥30	0.63	0.16	2.60	0.5262
Blood pressure				
Normal	1.00			
Pre-high BP	1.09	0.79	1.49	0.6022
High BP	1.11	0.78	1.59	0.5627
Total cholesterol (mg/dL)				

<200	1.00			
200-239	0.87	0.65	1.18	0.3809
≥240	0.73	0.43	1.26	0.2597
Hemoglobin				
Anemic	1.00			
Normocythemic	1.06	0.76	1.47	0.7454
Polycythemic	1.22	0.53	2.77	0.6438
Healthcare use				
None	1.00			
Hospitalizations	2.93	1.85	4.64	<.0001
ER visits	2.00	1.45	2.76	<.0001
ICU admissions	3.31	2.48	4.41	<.0001
Medication				
None	1.00			
Oral medication	0.32	0.15	0.71	0.0051
Inhaler + oral medication	0.37	0.18	0.76	0.0071
Number(#) of prescription				
<1/year	1.00			
1≤#≤2/year	1.26	0.59	2.71	0.5554
3≤#≤4/year	0.88	0.38	2.02	0.7598
≥5/year	0.67	0.29	1.56	0.3498
MPR				
< 20%	1.00			
20 ~ 39%	2.59	1.59	4.19	0.0001
40 ~ 59%	2.03	1.11	3.71	0.0207
60 ~ 79%	5.29	2.98	9.37	<.0001
≥ 80%	5.60	3.32	9.43	<.0001

COPD=chronic pulmonary obstructive disease; HR=hazards ratio; CI=confidence interval; BMI=body mass index; BP=blood pressure; ER=emergency room; ICU=intensive care unit; IVCS=intravenous corticosteroids; MPR=Medication possession ratio.

Table 9. Cox proportional hazards model for factors associated with respiratory disease-related mortality in patients with COPD

	HR	95% CI		P value
Gender				
Male	1.00			
Female	0.66	0.51	0.86	0.0022
Age				
40-49 years	1.00			
50-59 years	2.55	0.76	8.53	0.1298
60-69 years	4.19	1.32	13.30	0.015
70-79 years	10.36	3.28	32.70	<.0001
≥80 years	21.70	6.73	69.99	<.0001
Household income				
0~20%	1.00			
20~40%	1.06	0.79	1.41	0.7178
40~60%	0.95	0.70	1.29	0.7347
60~80%	0.98	0.73	1.31	0.8842
80~100%	0.88	0.67	1.15	0.3458
Region of residence				
Metropolitan	1.00			
Others	0.98	0.80	1.21	0.8793
Comorbidity				
None	1.00			
Hypertension	1.01	0.81	1.27	0.9132
Congestive heart failure	1.21	0.78	1.87	0.3927
Osteoporosis	0.74	0.46	1.20	0.2243
Diabetes mellitus	1.05	0.77	1.43	0.7573
Gastroesophageal reflux disease	1.09	0.80	1.49	0.5815
Hyperlipidemia	0.96	0.64	1.45	0.8391
Tuberculosis	1.55	1.10	2.20	0.0133
Smoking				

Never-smoker	1.00			
Ex-smoker	1.01	0.80	1.29	0.9112
Current-smoker	0.80	0.64	1.01	0.0586
BMI (kg/m^2)				
<18.5	2.06	1.64	2.58	<.0001
18.5-24.9	1.00			
25-29.9	0.67	0.51	0.89	0.0045
≥30	1.03	0.51	2.11	0.9304
Blood pressure				
Normal	1.00			
Pre-high BP	1.03	0.82	1.29	0.8167
High BP	1.04	0.81	1.34	0.7554
Total cholesterol (mg/dL)				
<200	1.00			
200-239	0.91	0.73	1.12	0.3639
≥240	0.97	0.70	1.34	0.8332
Hemoglobin				
Anemic	1.00			
Normocythemic	0.99	0.79	1.25	0.9498
Polycythemic	1.14	0.64	2.03	0.6463
Healthcare use				
None	1.00			
Hospitalizations	3.14	2.38	4.15	<.0001
ER visits	1.43	1.15	1.78	0.0015
ICU admissions	2.60	2.08	3.23	<.0001
Medication				
None	1.00			
Oral medication	0.55	0.35	0.89	0.0136
Inhaler + oral medication	0.45	0.29	0.71	0.0006
Number(#) of prescription				
<1/year	1.00			

1≤#≤2/year	1.10	0.73	1.65	0.655
3≤#≤4/year	0.76	0.48	1.20	0.238
≥5/year	0.61	0.38	0.99	0.0437
MPR				
< 20%	1.00			
20 ~ 39%	1.70	1.25	2.33	0.0009
40 ~ 59%	1.75	1.20	2.56	0.0036
60 ~ 79%	2.93	1.97	4.37	<.0001
≥ 80%	3.27	2.31	4.64	<.0001

COPD=chronic pulmonary obstructive disease; HR=hazards ratio; CI=confidence interval; BMI=body mass index; BP=blood pressure; ER=emergency room; ICU=intensive care unit; IVCS=intravenous corticosteroids; MPR=Medication possession ratio.

Table 10. Cox proportional hazards model for factors associated with other disease-related mortality except respiratory disease in patients with COPD

	HR	95% CI		P value
Gender				
Male	1.00			
Female	0.44	0.38	0.51	<.0001
Age				
40-49 years	1.00			
50-59 years	3.04	1.57	5.86	0.001
60-69 years	6.01	3.20	11.32	<.0001
70-79 years	12.64	6.73	23.76	<.0001
≥80 years	19.46	10.17	37.23	<.0001
Household income				
0~20%	1.00			
20~40%	1.02	0.86	1.21	0.7807
40~60%	0.95	0.79	1.13	0.5445

60~80%	0.88	0.75	1.05	0.1519
80~100%	0.88	0.75	1.02	0.0934
Region of residence				
Metropolitan	1.00			
Others	1.23	1.08	1.39	0.0013
Comorbidity				
None	1.00			
Hypertension	1.17	1.04	1.33	0.0102
Congestive heart failure	1.47	1.15	1.87	0.0022
Osteoporosis	1.16	0.92	1.44	0.206
Diabetes mellitus	1.34	1.15	1.56	0.0002
Gastroesophageal reflux disease	1.01	0.85	1.20	0.9564
Hyperlipidemia	1.04	0.84	1.27	0.7412
Tuberculosis	1.27	1.00	1.62	0.0524
Smoking				
Never-smoker	1.00			
Ex-smoker	0.96	0.82	1.12	0.5805
Current-smoker	1.34	1.18	1.52	<.0001
BMI (kg/m^2)				
<18.5	1.52	1.29	1.78	<.0001
18.5-24.9	1.00			
25-29.9	0.82	0.72	0.94	0.0042
≥30	0.90	0.61	1.33	0.6046
Blood pressure				
Normal	1.00			
Pre-high BP	1.00	0.87	1.14	0.9647
High BP	1.10	0.95	1.27	0.222
Total cholesterol (mg/dL)				
<200	1.00			
200-239	0.88	0.78	1.00	0.0522
≥240	1.01	0.84	1.21	0.9425

Hemoglobin				
Anemic	1.00			
Normocythemic	0.64	0.57	0.73	<.0001
Polycythemic	0.51	0.34	0.77	0.0015
Healthcare use				
None	1.00			
Hospitalizations	1.13	0.98	1.31	0.0992
ER visits	0.90	0.76	1.06	0.2133
ICU admissions	1.33	1.09	1.63	0.006
Medication				
None	1.00			
Oral medication	0.72	0.57	0.90	0.0042
Inhaler + oral medication	0.60	0.48	0.76	<.0001
Number(#) of prescription				
<1/year	1.00			
1≤#≤2/year	1.10	0.90	1.35	0.336
3≤#≤4/year	0.92	0.73	1.16	0.4699
≥5/year	0.54	0.42	0.70	<.0001
MPR				
< 20%	1.00			
20 ~ 39%	1.80	1.52	2.13	<.0001
40 ~ 59%	1.75	1.41	2.17	<.0001
60 ~ 79%	1.93	1.50	2.49	<.0001
≥ 80%	2.49	2.03	3.04	<.0001

COPD=chronic pulmonary obstructive disease; HR=hazards ratio; CI=confidence interval; BMI=body mass index; BP=blood pressure; ER=emergency room; ICU=intensive care unit; IVCS=intravenous corticosteroids; MPR=Medication possession ratio.

IV. DISCUSSION

In this study based on nationwide health screening database of South Korea, we showed the factors related to the mortality of COPD. The non-survivors in patients with COPD had the following features: male gender; older age; living in non-metropolitan area; more comorbidities; current smoker; lower BMI; lower hemoglobin; and more COPD medications and health care utilization.

Although the purpose of this study was not to analysis the mortality rate of COPD, the mortality rate of COPD was 78.7 per 100,000 person-years during the 12-year study period. Due to inconsistent COPD coding at the report of death and different use of diagnostic criteria, mortality data must be interpreted cautiously. Because we only included populations that were aged over 40 years and prescribed COPD medication, the mortality in this study might be overestimated. Generally, COPD mortality may be underestimated because of under-diagnosis problem. However, it is clear that COPD is one of the most important causes of death in most countries[20]. According to the World Health Organization, COPD is the fourth leading cause of death in the world. Approximately 2.7 million deaths from COPD occurred in 2000, half of them in the Western Pacific Region especially in China. Annually 400,000 deaths occur in developed countries[1]. In Europe, mortality rates are variable ranging from 20 to 80 per 100,000 populations[21]. However, according to the data from the First National Health and Nutrition Examination Survey (NHANES I) and NHANES III follow up studies, mortality rate is decreased by 15.8% for participants with moderate or severe COPD and 25.2% for those with mild COPD. Overall

mortality of COPD in the USA may be decreasing recently[22]. In China, COPD ranks as the fourth leading cause of death in urban areas and third leading in rural areas. Both crude and age-adjusted COPD mortality rates have fluctuated but have displayed a decreasing trend from 1990[23]. Mortality was high especially in very severe COPD patients in whom, 26% died after 1 year of follow-up, whereas 2.8% died among the non-COPD subjects[24].

Comorbidities of COPD contribute to worse patient-related outcome and the increase of health care utilization and mortality. The most well-known comorbidities include hypertension, ischemic heart disease, congestive heart failure, osteoporosis, depressive disorder, diabetes mellitus, arthritis, gastroesophageal reflux disease, hyperlipidemia, and anemia[25,26]. It is reported that about 80% of COPD patients have at least one comorbidity[27,28]. Several studies have reported that comorbidities of COPD contributed to an increased risk of mortality[29-31]. Similar to other studies, this study showed increased mortality in COPD with comorbidities. The burden of comorbidity measured by Charlson or COTE indices was associated with all-cause and respiratory-specific mortality in COPD[29,30]. The number of comorbidities was also linked to increased mortality[31].

Cardiovascular diseases are important comorbidity of COPD[32,33]. In this study, hypertension and congestive heart failure was associated with increased mortality in COPD patients. Ischemic heart disease, heart failure, and hypertension may be the most frequent and important diseases in COPD patients[33-35]. Poor outcomes including increased morbidity and mortality have been reported among patients with COPD and cardiovascular disease[33,36-38].

Heart failure and COPD are the important causes of admission, and each disease is a significant differential diagnosis for each other[35,37]. Congestive heart failure showed the highest odds ratio among the comorbidities in this study. Therefore, finding and treating heart failure in COPD patients is very important for better prognosis.

This study showed that tuberculosis was associated with increased COPD mortality. Tuberculosis has not considered an important comorbidity of COPD. However, a population-based study in Sweden reported that the relative risk of active tuberculosis was 3-fold higher in COPD patients[39]. They also reported that COPD patients with tuberculosis had a 2-fold increased risk for all-cause mortality within first year after diagnosis of tuberculosis. Korea is a country with a high incidence of tuberculosis. By the World Health Organization, the annual incidence of tuberculosis in Korea was 80 per 100,000 populations in 2015[40]. In our analysis, the risk of mortality in COPD patients was 2-fold higher in patients with tuberculosis.

It is unclear whether COPD medications affect the mortality. Our study showed a tendency to use more COPD medication in non-survivor group. The number of prescription and MPR were also higher in non-survivors. Oral COPD medication and intravenous corticosteroids were associated with increased mortality in COPD patients. Because severe COPD patients were prescribed more medications than non-severe COPD, the medications might be associated with increased mortality. Inhaled corticosteroids were recommended for patients with severe COPD or frequent exacerbations. Although numerous studies have reported the effect of inhaled corticosteroids, the impact of inhaled

corticosteroids on COPD mortality has shown a controversy. Some studies found no difference, but others found a reduction in COPD mortality[41]. However, a recent large-scale study (SUMMIT) has reported that the steroid inhaler did not affect mortality in patients with moderate COPD[42]. Long-acting beta agonists or long-acting muscarinic antagonists have been shown to improve lung function, reduce symptom and exacerbations[43-45]. However, the effect of these bronchodilators on COPD mortality is also unclear[46-48]. Two large randomized controlled trials have suggested that inhaler therapy improved COPD mortality. In the TORCH trial, the combination of salmeterol and fluticasone has shown the reduction of all-cause mortality compared with placebo although it was not statistically significant ($p=0.052$)[44,49]. In the UPLIFT trial, the mortality of COPD was significantly lower in the tiotropium group compared with placebo group[45]. The difference was only significant at day 1440, which was the predefined treatment period. However, including 30-day follow-up period, which was at day 1470, the difference was not significant.

Because low BMI or anemia reflects chronic illness and burden of disease, COPD patients with these conditions have an increased risk for poor outcomes. Our study also showed similar results. Low BMI or anemia was associated with increased mortality. The loss of fat free mass leads to muscle weakness and decreased exercise capacity in COPD patients. Studies have reported that low BMI in COPD patients was associated with increased mortality[50,51]. One report suggested that reversion of low body weight by appropriate therapy had a better effect on survival in COPD patients[52]. The prevalence of anemia in COPD

varies widely according to disease severity, age, or sex[53-55]. Studies have reported that a lower hematocrit was associated with an increased mortality[55-57]. Anemia is also a risk factor for long-term oxygen use in COPD patients[58]. Although anemia is a well-known comorbidity of COPD, studies on the impact of hemoglobin on COPD mortality are lacking, and the characteristics of populations in previous studies were highly variable. Although several studies have shown that anemia in COPD is related to increased mortality, to our knowledge, there are no studies that evaluated the association between anemia and long-term mortality of COPD in the general population.

Our study has some limitations. First, we could not use spirometry data. We used only ICD-10 codes and medications for COPD diagnosis. This might result in selection bias. However, Korean National Health Insurance only reimbursed the cost of inhaled long-acting bronchodilators when patients received the spirometry and satisfied the criteria of airflow limitation. Therefore, the physicians were implied to prescribe inhaled long-acting bronchodilator on the basis of the spirometry. Second, COPD patients without treatment could not be included. Relatively mild COPD patients without healthcare use might be excluded in the analysis. In addition to the features of COPD with under-diagnosis, this inclusion criterion might affect the low COPD prevalence of this study. Third, the diagnosis of comorbidity only based on ICD-10 code. Therefore, prevalence of comorbidity in our study might be different from other studies. Fourth, confounding factors could have affected the mortality. COPD mortality is associated with various factors. We attempted to control for possible confounders such as socioeconomic status, Charlson comorbidity index, BMI,

and smoking; however, other factors were not examined. Fifth, this is a retrospective observational study and so could involve missing data or follow-up loss. However, in the NHI database, every detail of healthcare utilization was recorded without any missing data. Moreover, since national insurance is mandatory by law, almost the entire population in Korea can be followed in the NHI database without loss. This advantage of the NHI database can increase the value of the results obtained in this study.

V. CONCLUSION

This study has showed a number of prognostic factors associated with COPD mortality. These clinical parameters may be useful to predict high risk COPD patients for poor prognosis. We also may achieve optimal management for COPD through the treatment of modifiable risk factors.

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ABSTRACT(IN KOREAN)

만성폐쇄성폐질환의 예후인자

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박선철

배경: 만성폐쇄성폐질환은 지속적인 기도 협착과 부분적인 가역성을 특징으로 보이는 질환이다. 전세계적으로 만성폐쇄성폐질환은 만성 질병 이환과 사망의 주요한 원인이다. 그러나 한국인에서는 만성폐쇄성폐질환의 사망률이나 예후인자가 잘 알려져 있지 않다. 본 연구의 목적은 대규모 인구 기반 자료를 이용하여 만성폐쇄성폐질환의 예후인자를 분석하는 것이다.

방법: 이 연구에서는 514,866 명의 건강검진코호트 자료를 이용하였다. 이 자료는 자격, 의료이용, 건강검진, 의료기관에 대한 정보를 포함하고 있다. 2002 년부터 2013 년도까지 40 세 이상의 만성폐쇄성폐질환 환자를 선별하였고 생존자와 사망자로 분류하였다. Cox 비례위험모형을 사용하여 만성폐쇄성폐질환의 사망과 관련된 독립위험인자들을 분석하였다.

결과: 총 21,622 명의 만성폐쇄성폐질환 환자가 포함되었고, 생존자는 16,757 명 사망자는 4,865 명이었다. 만성폐쇄성폐질환 환자의 평균 나이는 67.2 세였고, 남자가 63.5% 였다. 동반질환을 가지고 있는

고령의 남자에서 사망자가 많았다. 입원, 응급실 방문, 중환자실 입실, 만성폐쇄성폐질환 약물 사용과 같은 의료 이용 역시 사망자에서 더 많았다. 흡연, 저체중, 빈혈도 사망과 연관성을 보였다. 다변량분석에서 사망과 관련된 인자는 남성 (여성의 위험비 0.48, 95% 신뢰구간 0.42-0.55), 고령 (50-59 세의 위험비 2.91, 95% 신뢰구간 1.63-5.19; 60-69 세의 위험비 5.54, 95% 신뢰구간 3.18-9.66; 70-79 세의 위험비 12.05, 95% 신뢰구간 6.93-20.95; 80 세 이상의 위험비 20.29, 95% 신뢰구간 11.51-35.77), 대도시 외에 거주 (위험비 1.16, 95% 신뢰구간 1.04-1.29), 많은 동반질환 (고혈압의 위험비 1.14, 95% 신뢰구간 1.02-1.27; 울혈성심부전의 위험비 1.39, 95% 신뢰구간 1.12-1.71; 당뇨의 위험비 1.27, 95% 신뢰구간 1.11-1.46; 결핵의 위험비 1.34, 95% 신뢰구간 1.10-1.63), 높은 의료이용 (입원의 위험비 1.35, 95% 신뢰구간 1.19-1.54; 중환자실 입실의 위험비 1.80, 95% 신뢰구간 1.56-2.09), 현재 흡연 (위험비 1.18, 95% 신뢰구간 1.06-1.32), 저체중 (위험비 1.67, 95% 신뢰구간 1.47-1.91), 낮은 혈색소 (정상 혈색소의 위험비 0.71, 95% 신뢰구간 0.64-0.79)였다.

결론: 본 연구는 만성폐쇄성폐질환과 관련된 예후인자들을 보여주었으며, 이러한 인자들을 통해 고위험의 만성폐쇄성폐질환 환자를 선별할 수 있다. 또한 교정이 가능한 인자들을 조절함으로써 만성폐쇄성폐질환에 대한 최적의 치료를 할 수 있다.

핵심되는 말: 만성폐쇄성폐질환, 사망, 예후인자, 동반질환, 의료이용, 건강검진