보건학 석사학위논문

Risk of acute exacerbation and severe acute exacerbation associated with different severities of COPD at diagnosis

만성 폐쇄성 폐질환 진단 시 중증도에 따른 급성 악화 및 중증 급성 악화 발생위험비교를 위한 연구

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보건학과 역학 전공

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이 논문을 보건학 석사학위논문으로 제출함

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ABSTRACT

Risk of acute exacerbation and severe acute exacerbation associated with different severities of COPD at diagnosis

: a prospective cohort study in Korea

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Background: COPD is the most common respiratory disease worldwide and also is a major cause of morbidity and mortality throughout the world which imposes important challenge to public health. Despite increasing societal burden of COPD, it is widely

under-recognised and under-diagnosed by both the patients and physicians due to various reasons including the low usage of pulmonary function tests(PFTs). However recent studies suggest that the decline of lung function in COPD patients occur in the earlier course of the disease than previously thought, which suggest implementation of aggressive testing to avoid delay in diagnosis and respective initiation of treatments. This study aims to assess the difference in health outcomes, specifically acute exacerbation and severe acute exacerbation between the patients diagnosed at varying severities of COPD.

Methods: This prospective cohort study used the National Health Insurance Service-National Sample Cohort(NHIS-NSC) to enroll newly diagnosed COPD patients with varying disease severities of mild, moderate and severe COPD between 2006 and 2007, then the patients were followed up for events of acute exacerbation and severe acute exacerbation until 31st December 2013.

Results: Total of 1,280 patients which consisted of 685 of patients diagnosed as mild COPD, 383 of patients diagnosed as moderate COPD, 212 of patients diagnosed as severe COPD. When compared to patients diagnosed as mild COPD, the risk of acute exacerbation was higher for patients diagnosed as moderate COPD (unadjusted HR:

1.13, 95% CI: 0.70-1.82; adjusted HR: 1.07, 95% CI: 0.72-1.59) and more dramatically with patients diagnosed as severe COPD (unadjusted HR: 2.45, 95% CI: 1.54-3.88; adjusted HR: 2.12, 95% CI: 1.43-3.14). The risk of severe acute exacerbation was also higher for patients diagnosed as moderate COPD (unadjusted HR: 1.45, 95% CI: 0.99-2.13; adjusted HR: 1.36, 95% CI: 0.94-1.96) and for patients diagnosed as severe COPD (unadjusted HR: 2.94, 95% CI: 2.02-4.29; adjusted HR: 2.56, 95% CI: 1.77-3.71) when compared to the patients diagnosed as mild COPD .

Conclusions: The risk of acute exacerbation and severe acute exacerbation was increased in patients diagnosed as moderate COPD and more dramatically with patients diagnosed as severe COPD when compared to patients with mild COPD at diagnosis, which may contribute as an evidence to enhancing importance of early diagnosis in COPD.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, severe acute exacerbation, early diagnosis, large claims database, prospective cohort

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1. Introduction

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD) by definition is a disease characterised by restricted airway and persistent respiratory symptoms which is due to airway abnormalities caused by considerable exposure to mainly tobacco smoke or other air pollutants. These noxious gases cause chronic inflammation in small airways and destruction of parenchyma in susceptible individuals which collectively leads to a chronic airflow limitation and hence to a decline in overall lung function. The most characteristic symptom of COPD predictably is chronic dyspnoea and also up to one third of patients experience cough and sputum production. However airflow limitation could also be present without any detectable symptoms and as the decision to seek medical attention is usually made only when the patient's functional status is significantly impaired(1), there is a potential risk of considerable delay in diagnosis of COPD in practice.

COPD is the most common respiratory disease worldwide and also

is a major cause of morbidity and mortality throughout the world(2). Similar trend is observed in Korea with the prevalence as high as 14.2% in ≥40 years old and 31% in ≥65 years old and the burden of disease is reported to be substantial which scored 5th of top 10 burden of disease in Korea(3). COPD imposes an important challenge to public health however its burden is projected to increase only higher because of aging population and continued exposure to associated risk factors(1).

Despite increasing societal burden of COPD, it is widely under-recognised and under-diagnosed by both the patients and physicians due to the low usage of pulmonary function tests(PFTs), lack of awareness of the disease, poor physician adherence to guidelines and lack of education programs of COPD. Chung et al analysed the Korean Health and Nutritional Examination survey and reported that out of 897 patients with airway obstruction, only 3% were diagnosed by the physician and the rest were undiagnosed which ascertained marked under-diagnosis of COPD in Korea(4).

Not only diagnosis of COPD is under-performed but also acute exacerbation of COPD is also under-reported. Acute exacerbation of

COPD is an acute worsening of respiratory symptom that results in additional therapy and it is a particularly important event for COPD patients as it negatively impacts their health which in severe cases can cause acute respiratory failure. Therefore their management and appropriate plans to minimise future acute exacerbation risk is critical, However despite its significance it is under-reported due to the lack of awareness on symptoms and lack of education on its importance of management and when to seek medical attention(1).

Traditionally COPD was considered progressive and irreversible disease that responds poorly to treatments with the sole treatment which can alter the course of disease being smoking cessation(5). However since 2006, GOLD guideline defined COPD as "preventable" and "treatable" disease(1) which means that early detection and treatment of disease has become more important. Also recent studies suggest that the decline of lung function in COPD patients occur in the earlier course of the disease than previously thought. Tantucci et al(6) reported that the mean rate of forced expiratory volume in 1 second(FEV1) decline was found out to be among patients in GOLD Stage II and III patients which contrasted to slower decline in more advanced disease (Figure 1). Also Drummond et al(7) reviewed the

longitudinal study of mild-to moderate COPD patients which reported a rapid decline in lung function in moderate stage COPD patients. These results collectively suggest aggressive testing to avoid delay in diagnosis and respective initiation of treatments such as smoking cessation needs to be implemented.

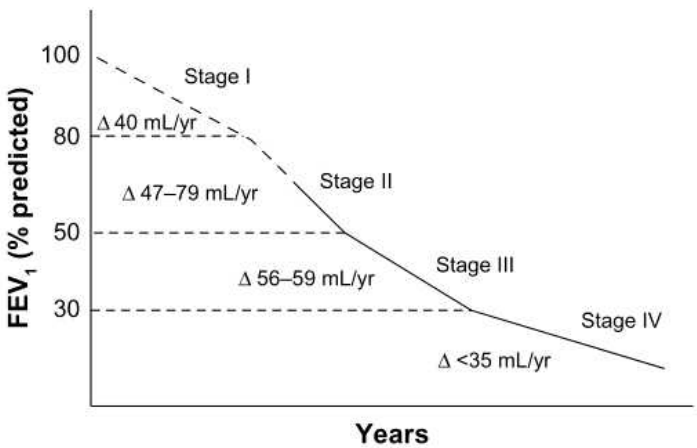

Figure 1. Recent evaluation of rate of decline in lung function in patients with chronic obstructive pulmonary disease demonstrating that the largest rate of decline in lung function may occur in moderate disease. (6)

1.2 Literature review

In light of increasing importance of early diagnosis and treatment of COPD there has been number of studies which reviewed the evidences that support the early diagnosis of COPD.

Importance of early diagnosis in COPD

COPD is characterised by the presence of multiple inflammatory mediators and they tend to increase as the severity of the disease becomes more critical. However this inflammation within the airway is also observed in the early asymptomatic COPD patients which means when the symptoms of COPD becomes apparent it may be too late to control(8). In 2008, Johansson et al reported that treating early COPD patients with limited symptoms is more effective in controlling various complications such as dyspnoea and acute exacerbations associated with the progressive COPD. When 244 mild COPD patients were treated with tiotropium for 12 weeks on randomised double-blind placebo-controlled trial, compared to the placebo arm patients treated with tiotropium showed statistical improvement in both FEV1 and FVC(Forced Vital Capacity) (Figure 2.)(9). Celli et al also reported that the pharmacotherapy has indeed reduced the rate of

decline of FEV1 in patients with moderate-severe COPD patients, slowing down the disease progression(10). This demonstrates the appropriate use of the treatment should be implemented as early as possible to slow down the overall disease progression of COPD.

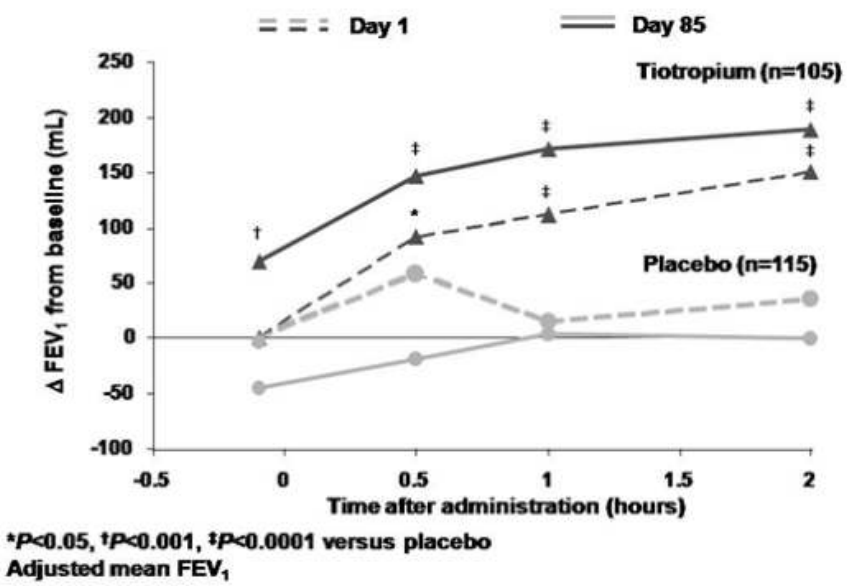

Figure 2. The peak improvements in FEV 1 over 2 hours of tiotropium is a significant difference compared with placebo over the 2-hour at all points. (9)

1.3 Rationale for the study

As outlined above, COPD is the most common respiratory disease which is associated with paramount social burden due to its high morbidity and mortality which WHO projected by 2020 will be the 3rd leading cause of death worldwide. Despite this COPD is highly under-recognised and under-diagnosed disease mainly due to the low usage of PFTs and low disease awareness both by the patients and physicians. As traditionally COPD was defined as irreversible disease and also as until recently it was not widely known that the decline in the lung function in fact happens in the earlier stage of the disease, therefore treatment in early COPD has been under-appreciated. However as the evidence of importance of treating early COPD accumulated there has been several studies assessing the efficacy of pharmacotherapies in early COPD patients, but there has not been a study which assessed the difference in resultant health outcomes between the patients diagnosed as early-stage COPD and late-stage COPD in real-life setting.

1.4 Study objectives

Therefore this study aims to assess the difference in the health outcomes, specifically acute exacerbation and severe acute exacerbation between the patients diagnosed at varying severities of COPD. Acute exacerbation and severe acute exacerbation were selected as they not only impose negative health impacts on COPD patients but also are responsible for biggest portion of social burden especially for severe acute exacerbation as it increases the risk of death. The analysis was carried out using the claims data obtained from Korean National Health Insurance Services in the form of 13-year(2002~2013) cohort data comprised of 1 million Korean patients (2% of the whole population) which is validated to be appropriate representative of Korean population(11).

Specific objectives of this study were as follows:

First, assess the difference in acute exacerbation risk between patients diagnosed as mild, moderate and severe COPD

Second, assess the difference in severe acute exacerbation risk between patients diagnosed as mild, moderate and severe COPD

2. Methods

2.1 Data source

This study used the National Health Insurance Service-National Sample Cohort(NHIS-NSC) which is a population based cohort established by the National Health Insurance Service(NHIS) in Korea(NHIS-2017-2-374). The NHIS-NSC consists of approximately 1 million participants who were randomly sampled from 2002 Korean health insurance database to obtain baseline data. Cohort is followed for total of 13 years(2002~2013) and during the follow-up a representative sample of newborns was added annually and deceased or emigrated participants were removed from the population (Figure 3)(11).

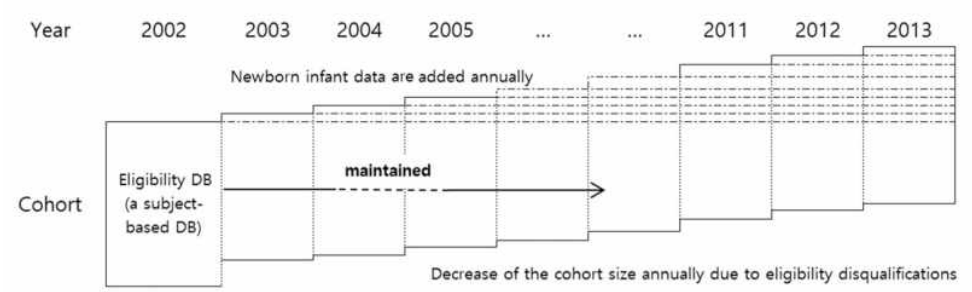

Figure 3. Schematic representation of the cohort data construction. (11)

The NHIS-NSC comprises of four databases which include participant's insurance eligibility, medical treatments, medical care institutions and general health examination as shown in Figure 4 below.

The NHIS-NSC was chosen as a data source for this study as it is 13-year cohort data which provides long enough time to observe events of interest in this study which are acute exacerbations and severe acute exacerbations as they do not usually occur within short period of time which previous study allowed 3 years to observe acute exacerbation frequencies(12). Also, it provides treatment details which can be utilised to define the severity of COPD at diagnosis.

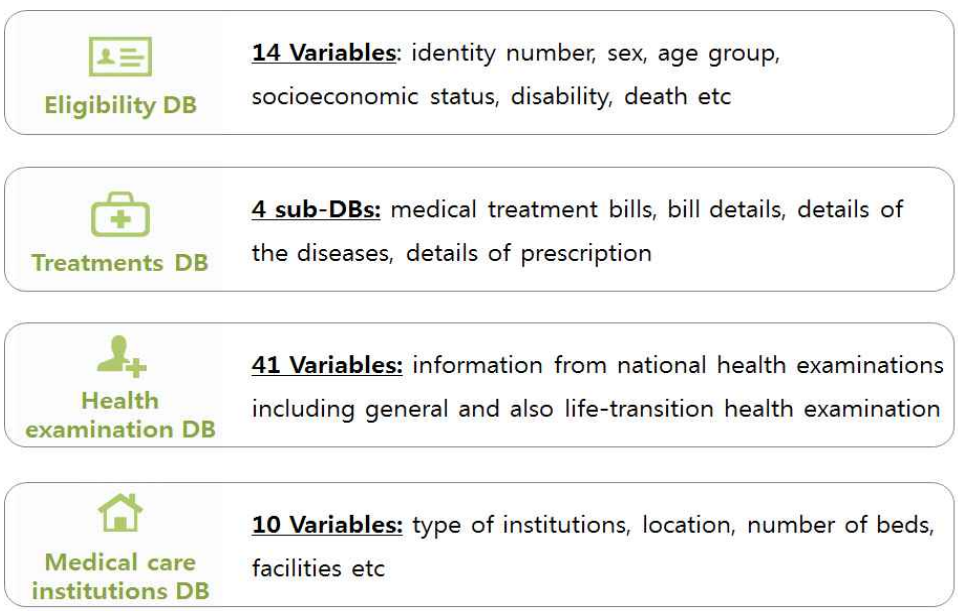

Figure 4. Composition of databases of NHIS-NSC. (11)

2.2 Study design

This study is a prospective cohort study which aims to assess the difference in risk of acute exacerbation and severe acute exacerbation between patients diagnosed as mild, moderate and severe COPD. As the target population is the newly diagnosed COPD patients with different severity of the disease, those patients who have no history of COPD between 1st January 2002~ 31st December 2005 were selected first, then the patients who fulfill the COPD diagnosis criteria (Table 1. in "2.3.1 Newly diagnosed COPD patients" section) between 1st January 2006~ 31st December 2007 were then selected. Selected patients were divided into 3 groups of disease severity which are mild, moderate, or severe COPD according to the treatment they received on diagnosis(Table 2. in "2.3.2 Severity of COPD at diagnosis" section). It was assumed that there was no misclassification of the severity of COPD at diagnosis however possible impacts of misclassification was assessed through sensitivity analysis. Selected patients were followed up for event of acute exacerbation or severe acute exacerbation until the event occurrence then the follow-up was ceased(definition of events are provided in "2.4.2 Dependent Variable" section). If the events did not occur then

the follow-up ended on 31st December 2013 (Figure 5, 6). When the follow-up for all patients was complete, the risk of acute exacerbation and severe acute exacerbation was assessed for each of the severity groups.

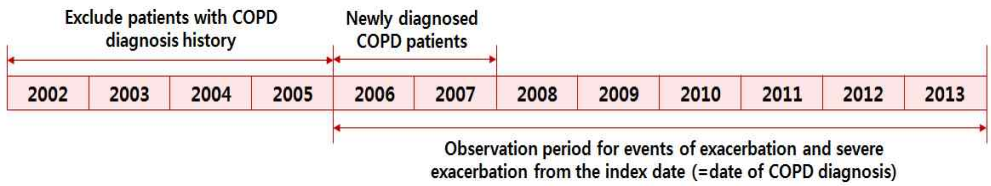

Figure 5. Cohort construction of the study

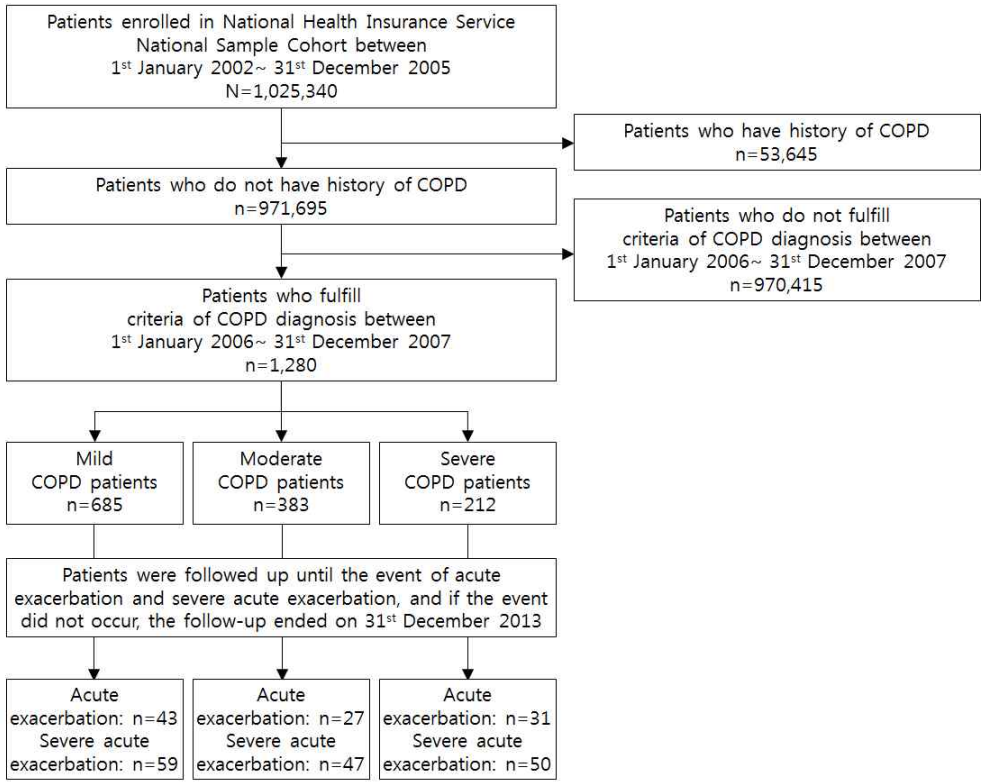

Figure 6. Patient flow of the study

2.3 Study population

This study aimed to assess the risk of acute exacerbation and severe acute exacerbation between patients diagnosed as mild, moderate and severe COPD, therefore the target population for this study was patients diagnosed as mild, moderate and severe COPD.

2.3.1 Newly diagnosed COPD patients

In order to select the newly diagnosed COPD patients, this study utilised the operational definition of COPD diagnosis locally developed by Lee et al. which can be utilised when conducting studies using claims data(Table 1)(13) and this operational definition is similar to the operational definition of COPD used in studies using claims data in other countries(25, 26, 27).

Table 1. Operational definition of diagnosis of COPD

A COPD patient was defined by the following criteria:
1) Age greater than 40 years
2) ICD-10 codes for COPD or emphysema (J42.x-J44.x, except J430)
3) Use of more than one drug for COPD at least twice per year

[long-acting muscarinic antagonist (LAMA), long-acting beta-2 agonist (LABA), inhaled corticosteroids (ICS), ICS plus LABA (ICS+LABA), short-acting muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA)]

2.3.2 Severity of COPD at diagnosis

According to the most widely used COPD guideline, GOLD guideline, when patient is diagnosed as COPD multiple factors such as symptomatic assessment, spirometric classification and/or risk of acute exacerbation are taken into consideration when their severity of the disease is assessed (Figure 7)(1).

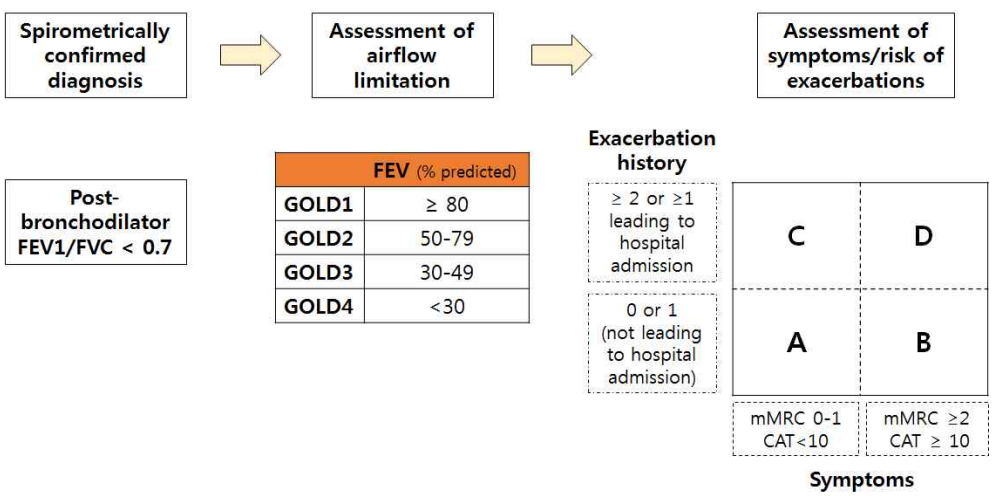

Figure 7. COPD assessment tool. (1)

However as the data source (NHIS-NSC) does not contain spirometric assesment results nor it contains symptomatic assesment results, the difference in treatment decision for COPD patients for different level of severity was employed to differentiate the severity of the disease for newly diagnosed patients.

In order to define the severity of the COPD at diagnosis using treatment decision, COPD guideline published in 2006 was used because our study enrolled the newly diagnosed patients between 2006 and 2007. The treatment guidance provided by the COPD guideline is as below (Figure 8)(14).

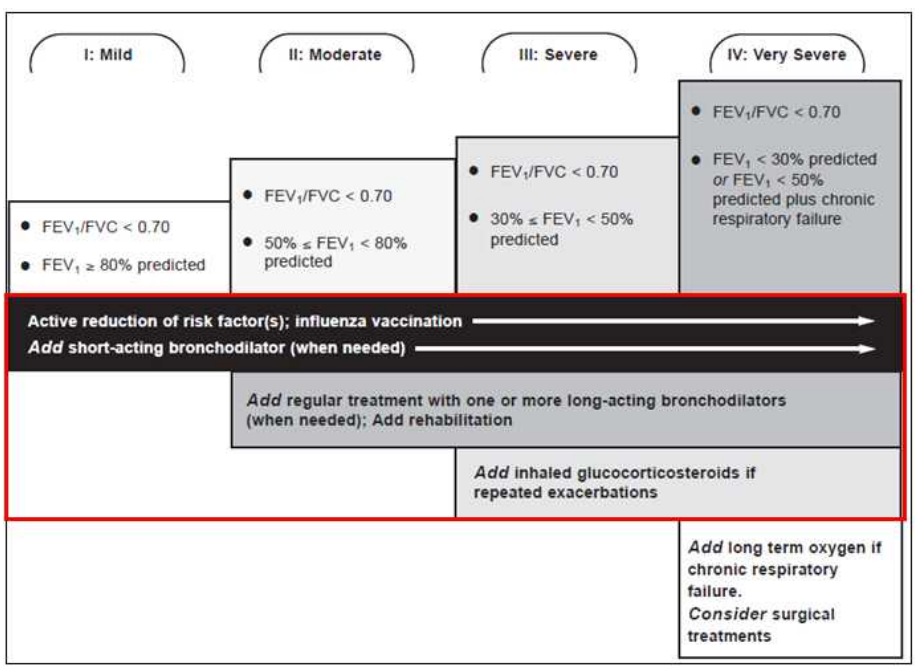

Figure 8. Treatment pattern according to the COPD severity (14)

Following the above treatment guidance the severity of the COPD patients at diagnosis is defined as below Table 2.:

Table 2. Severity of the COPD patients at diagnosis

1. **Mild COPD**: patient who were prescribed with SABA(short acting beta2 agonist) or SAMA(short acting muscarinic antagonist) at diagnosis
2. **Moderate COPD**: patient who were prescribed with LABA(long acting beta2 agonist) or LAMA(long acting muscarinic antagonist) or LABA+LAMA at diagnosis
3. **Severe COPD**: patient who were prescribed with LABA+ICS(inhaled corticosteroid) or LABA+ICS+LAMA at diagnosis

The list of drugs used to define the diagnosis of COPD and also the severity of COPD is provided in Appendix 1.

2.4 Study variables

2.4.1 Independent variables

Independent variable included in this study are as below:

1. **Sex (variable code- SEX):** Male, female

2. **Age group (variable code- AGE_GROUP):** 40~49 years old, 50~59 years old, 60~69 years old, 70~79 years old, 80 years old and over

3. **Smoking (variable code- SMK_STAT_TYPE_RSPS_CD):** never smoker, previous smoker or current smoker, unknown

4. **Income level (variable code- CTRB-PT-TYPE-CD):** level 0~4, level 5~7, level 8~10

5. **Co-morbidities known to be associated with acute exacerbation(1) (variable code- MAIN_SICK, SUB_SICK):** gastro-oesophageal reflux disease(GERD) (ICD-10 code: K21.x),

pneumonia (ICD-10 code: J12.x, J13, J14, J15.x, J16.x, J17.x), thrombosis (ICD-10 code: I74.x), heart failure (ICD-10 code: I50.x), depression (ICD-10 code: F32.x, F33.x), bronchitis (ICD-10 code: J41.x), atrial fibrillation (ICD-10 code: I48)

2.4.2 Dependent Variable

Dependent variables of the study are acute exacerbation event and severe acute exacerbation event. According to the GOLD guideline acute exacerbation is defined as an acute worsening of respiratory symptom that results in additional therapy and GOLD guideline also provides the definition of severe acute exacerbation as an acute exacerbation which requires hospitalisation. These events are temporary and usually reversible events which should not be confused with exacerbation of the disease itself which happens as a natural clinical course of the disease. As acute exacerbation is mainly triggered by respiratory viral and/or bacterial infections and as during acute exacerbation event the airway inflammation is increased acute exacerbation events are normally treated with systemic antibiotics and/or oral corticosteroids which this definition was adopted by other

studies(1)(12). Therefore in this study the dependent variables, acute exacerbation and severe acute exacerbation events are defined as below, and compared to other studies using claims data, this definition is more stricter as for example other studies defined acute exacerbation as COPD diagnosis with oral corticosteroids (25,26,27).

1. Acute exacerbation:

a) ICD-10 codes for COPD or emphysema (J42.x-J44.x, except J430) AND

b) use of oral or injectable steroids AND

c) use of oral or injectable antibiotics (amoxicillin, amoxicillin/clavulanate, doxycycline, cephalosporin(cefuroxime, cefpodoxime, cefdinir, cefprozil), advanced macrolide(azithromycine, clarithromycin, roxythromycin), fluoroquinolone(moxifloxacine, gemifloxacine, levofloxacine)

* list of steroids and antibiotics provided in Appendix 2 and 3.

2. Severe acute exacerbation:

a) ICD-10 codes for COPD or emphysema (J42.x-J44.x, except J430) AND

b) use of oral or injectable steroids AND

c) use of oral or injectable antibiotics (amoxicillin, amoxicillin/clavulanate, doxycycline, cephalosporin(cefuroxime, cefpodoxime, cefdinir, cefprozil), advanced macrolide(azithromycine, clarithromycin, roxythromycin), fluoroquinolone(moxifloxacine, gemifloxacine, levofloxacine) AND

d) hospitalisation (variable code- FST_IN_PAT_DT)

2.4.3 Covariates

Independent variables mentioned in section 2.3.1 were considered potential confounding factors.

2.5 Statistical analysis

All statistical analysis for this study were carried out using SAS version 9.4 (SAS Institute, Cary, NC) and the significance level were set as 5%. The demographic characteristics were provided in the form of frequency and percentage, and the difference of demographic characteristics between different severities of COPD at diagnosis was carried out using student t-test or chi-square test. Incidence proportion and incidence rate per 1,000 person-year for acute exacerbation and severe acute exacerbation was calculated and its 95% confidence interval was provided. The primary endpoint of the study which is risk of acute exacerbation and severe acute exacerbation between different severities of COPD at diagnosis was carried out using Cox proportional hazard model and potential confounding factors were adjusted. Sensitivity analysis was also carried out in order to assess the possible impacts of misclassification of severity of COPD at diagnosis.

2.5.1 Baseline analysis of study population

- All demographic characteristics are discrete variables therefore they are provided in the form of frequency and percentage.

- The difference of demographic characteristics between mild, moderate and severe COPD patients were analysed using chi-square test.

2.5.2 Incidence proportion and incidence rates of acute exacerbation and severe acute exacerbation

- Incidence proportion and incidence rate per 1000 person-year of acute exacerbation and severe acute exacerbation were analysed. The start-date of follow-up is the date of COPD diagnosis and the end-date of follow-up is the date of event or if the event did not occur then the end-date is 31st December 2013. Using the total follow-up period, person-year was calculated and incidence proportion and incidence rate per 1000 perosn-year were calculated accordingly.

- Incidence rate per 1000 person-year = [acute exacerbation (or severe acute exacerbation) cases / person-years] x 1,000

- 95% confidence interval of incidence rate

$$= IRc \pm 1.96 \times [\frac{IRc}{n}]^{\left(\frac{1}{2}\right)}$$

IRc=crude incidence rate

n=denominator of the rate

2.5.3 Risk of acute exacerbation and severe acute exacerbation between mild, moderate and severe COPD patients diagnosis

Risk of acute exacerbation and severe acute exacerbation between mild, moderate and severe COPD patients were calculated using the mild COPD patients as a reference. The statistical model used was Cox proportional hazard model, and to assess whether the hazard functions are proportional over time their log-log plots were evaluated and also the null hypothesis that proportional hazards assumption is valid was tested. The risk of acute exacerbation and severe acute exacerbations were analysed as hazard ratio (HR) with their 95% confidence interval. The potential confounding factors which are sex,

age group, smoking, income level, co-morbidities known to be associated with acute exacerbation were also used as adjustment factors to generate adjusted hazard ratio.

2.5.4 Stratified analysis

Stratified analysis using confounding factors, which are sex, age group, smoking, income level, co-morbidities known to be associated with acute exacerbation, were carried out for all the above analysis in order to assess the potential impact of confounding factors.

2.5.5 Sensitivity analysis

Sensitivity analysis was carried out for the independent variables that can impact the outcome, and in this study sensitivity analysis was carried out for 3 different variables especially to control inherent limitation of claims data.

(1) Smoking

Although other environmental exposures such as biomass fuel exposure and air pollution may contribute, smoking is still the main risk factor for COPD(1). Therefore in order to assess the possible

impact of misclassification false-COPD patients being enrolled to the study, analysis excluding the never-smoker was carried out.

(2) COPD diagnosis criteria

This study employed the COPD diagnosis criteria from the previous local study which can be used when analysing the claims data, and this criteria was similar to the COPD diagnosis criteria used by studies from other countries when using claims data. However, in order to assess the specificity of this criteria, sensitivity analysis was carried out using more strict criteria of below:

- 3 or more individual COPD prescriptions per year
- 4 or more individual COPD prescriptions per year
- 2 or more individual COPD prescriptions per year and each prescription with at least 30 days of duration
- 2 or more individual COPD prescriptions per year and each prescription with at least 60 days of duration

(3) Baseline severity

Rather than the result of pulmonary function test(PFT), due to the absence of PFT results in the data source, the severity of the COPD in this study was decided by the treatment used at diagnosis

according to the GOLD guideline. However, there could be chance of patients' severity of COPD being misclassified. Therefore in order to assess the impact of misclassification of baseline severity, change of severity at follow up year 1, 3, and 5 as compared to year 0 of base year before the event of acute exacerbation or severe acute exacerbation was analysed. As the change in severity after the event may be impacted by the natural clinical course of the disease, these patients were excluded from this sensitivity analysis. For the purpose of assessing the impact of misclassification that can result in strengthening the dependent variable, excluding over-prescribed patients especially when there was no COPD medication prescribed in the follow-up years was assessed.

3. Results

3.1 Study population

The patients who were enrolled in National Health Insurance Service- National Sample Cohort from 1st January 2002 to 31st December 2005 was total of 1,025,340. From this pool of patients, patients who have history of COPD(n=53,645) were excluded. Out of remaining patients, the patient who fulfill the criteria of COPD diagnosis(Table 1.) from 1st January 2006 to 31st December 2007 (n=1,280) were extracted to form newly diagnosed COPD patients. From this cohort newly diagnosed COPD patients, when they were divided according to their severity of the disease at COPD diagnosis, there were 685 “mild COPD” patients, 383 “moderate COPD” patients, and 212 “severe COPD” patients (Figure 6.).

3.2 Baseline characteristics of study population

Baseline characteristics which are sex, age group, smoking, income level, and co-morbidities known to be associated with acute exacerbation were analysed for mild, moderate and severe COPD patients.(Table 3.)

For all groups, number of male patients were higher compared to female patients which the difference was statistically significant (p=0.0014). The difference between the male and female patients was the biggest for patients diagnosed as severe COPD(33.02%) which the number of male patients was almost double(male vs. female; 66.51% vs. 33.49%).

The most prevalent age group was 60~69 years old for mild and severe COPD groups (30.51% and 35.38% respectively), and was 70~79 year old for moderate COPD group (31.33%), however the overall difference between the groups were not statistically significant (p=0.43).

For approximately 20% patients, the smoking status was unknown and for the patients whose smoking status are known, there were more never smokers compared to previous or current smokers.

The most frequently observed income level was level 8~10 for all

groups which was 42.34%, 42.82%, 41.98% for mild, moderate and severe COPD group, however the overall difference between the groups were not statistically significant (p=0.48).

For co-morbidities known to be associated with acute exacerbation, the most frequently observed co-morbidity for mild and severe COPD group was bronchitis (31.85%, 35.98% respectively), and gastro-oesophageal reflux disease for mild COPD group (29.35%), however the overall difference between the groups were not statistically significant (p=0.66).

Table 3. Baseline characteristics of study population

	Mild COPD n=685	Moderate COPD n=383	Severe COPD n=212	P-value
Sex (%)				0.0014
- Male	369 (53.87)	236 (61.26)	141 (66.51)	
- Female	316 (46.13)	147 (38.38)	71 (33.49)	
Age group (%)				0.43
- 40~49 years old	95 (13.87)	43 (11.23)	21 (9.91)	
- 50~59 years old	121 (17.66)	74 (19.32)	38 (17.92)	

- 60~69 years old	209 (30.51)	115 (30.03)	75 (35.38)	
- 70~79 years old	186 (27.15)	120 (31.33)	59 (27.83)	
- 80 years old or more	74 (10.80)	31 (8.09)	19 (8.96)	
Smoking (%)				0.1326
- never smoker	384 (56.06)	195 (50.91)	99 (46.70)	
- previous smoker	38 (5.55)	23 (6.01)	20 (9.43)	
- current smoker	116 (16.93)	80 (20.89)	43 (20.28)	
- unknown	147 (21.46)	85 (22.19)	50 (23.58)	
Income level (%)				0.48
- 0~3	217 (31.68)	118 (30.81)	56 (26.42)	
- 4~7	178 (25.99)	101 (26.37)	67 (31.60)	
- 8~10	290 (42.34)	164 (42.82)	89 (41.98)	
Co-morbidities known to be associated with exacerbation (%)				0.66
- Atrial fibrillation	3 (2.22)	4 (4.35)	3 (6.25)	
- GERD	40 (29.63)	27 (29.35)	8 (16.67)	
- Pneumonia	15 (11.11)	15 (16.30)	7 (14.58)	
- Heart Failure	20 (14.81)	12 (13.04)	6 (12.50)	
- Thromboembolism	1 (0.74)	0 (0.00)	0 (0.00)	
- Depression	13 (9.63)	9 (9.78)	5 (10.42)	
- Bronchitis	43 (31.85)	25 (27.17)	19 (39.58)	

3.3 Incidence proportion and incidence rates of acute exacerbation and severe acute exacerbation

3.3.1 Incidence proportion and incidence rate of acute exacerbation

There was no difference in incidence proportion and incidence rate of acute exacerbation between male and female patients(male vs. female; 8% vs. 8%, 11.99 vs. 11.92) and the incidence proportion and incidence rate of acute exacerbation were the highest for 60-69 years old patients (10%, 14.69).

The incidence proportion and incidence rate of acute exacerbation was higher in previous or current smoker (17%, 28.20) compared to non-smoker patients (11%, 17.28).

Incidence proportion and incidence rate of acute exacerbation was higher for previous or current smokers compared to never smokers.

Among the 3 groups of income level, the level 4~7 patients showed the highest incidence proportion and incidence rate of acute exacerbation (10%, 14.68).

For co-morbidities known to be associated with acute exacerbation, bronchitis showed the highest incidence proportion and incidence rate of acute exacerbation (11%, 17.79).

For different severities of COPD at diagnosis, the incidence proportion and incidence rate of acute exacerbation showed the increasing trend as the severity of COPD at diagnosis increased from mild to moderate to severe (6%, 7%, 15% respectively for incidence proportion, 9.36, 10.61, 23.67 respectively for incidence rate).

Table 4. Incidence proportion(IP) and incidence rate(IR) of acute exacerbation

	Total (n)	No. of p-y**	Event (n)	IP (%)*	IR per 1000 p-y (95% CI)
Sex					
- Male	746	4922	59	8%	11.99 (8.93-15.04)
- Female	534	3524	42	8%	11.92 (8.31-15.51)
Age group					
- 40~49 years old	159	1046	14	9%	13.39 (6.38-10.40)
- 50~59 years old	233	1558	14	6%	8.99 (4.28-13.69)
- 60~69 years old	399	2586	38	10%	14.69 (10.02-19.36)
- 70~79 years old	365	2399	30	8%	12.51 (8.03-16.98)
- 80 years old or more	124	858	5	4%	5.83 (0.72-10.94)

Smoking (%)					
- never smoker	678	4294	79	11.7%	18.40 (14.34-22.45)
- previous or current smoker	320	1964	46	14.4%	23.42 (16.65-30.19)
- unknown	282	1852	24	8.5%	12.96 (7.77-18.14)
Income level					
- 0-3	391	2605	28	7%	10.75 (6.77-14.73)
- 4~7	346	2248	33	10%	14.68 (9.67-19.69)
- 8~10	543	3594	40	7%	11.13 (7.68-14.58)
Co-morbidities known to be associated with exacerbation					
- Atrial fibrillation	10	65	1	10%	15.49 (-14.87-45.84)
- GERD	75	507	2	3%	3.95 (-1.52-9.42)
- Pneumonia	37	237	2	5%	8.45 (-3.26-20.17)
- Heart Failure	38	247	4	11%	16.22 (0.32-32.11)
- Thrombo-embolism	1	7	0	0%	0.00
- Depression	27	190	0	0%	0.00
- Bronchitis	87	562	10	11%	17.79 (6.77-28.82)
Severity of COPD at diagnosis					
- Mild	685	4592	43	6%	9.36 (6.57-12.16)

- Moderate	383	2545	27	7%	10.61 (6.61-14.61)
- Severe	212	1309	31	15%	23.67 (15.34-32.01)

* Incidence proportion(IP)= event/total

** p-y= person-year

3.3.2 Incidence proportion and incidence rate of severe acute exacerbation

Both the incidence proportion and incidence rate of severe acute exacerbation were more than double for male patients compared to female patients(male vs. female; 16% vs. 7%, 24.34 vs. 10.44) and the incidence proportion and incidence rate of severe acute exacerbation were the highest for 70~79 years old patients (16%, 25.67).

The incidence proportion and incidence rate of severe acute exacerbation was higher in previous or current smoker (15%, 22.98) compared to never smoker patients (11%, 17.03).

Among the 3 groups of income level, the level 4~7 patients showed the highest incidence proportion and incidence rate of severe acute exacerbation (14%, 21.16).

For co-morbidities known to be associated with acute exacerbation,

pneumonia showed the highest incidence proportion and incidence rate of severe acute exacerbation (19%, 31.67).

For different severities of COPD at diagnosis, the incidence proportion and incidence rate of severe acute exacerbation showed the increasing trend as the severity of COPD at diagnosis increased from mild to moderate to severe (9%, 12%, 24% respectively for incidence proportion, 12.76, 18.53, 37.63 respectively for incidence rate).

Table 5. Incidence proportion(IP) and incidence rate(IR) of severe acute exacerbation

	Total (n)	No. of p-y**	Event (n)	IP* (%)	IR per 1000 p-y (95% CI)
Sex					
- Male	746	4849	118	16%	24.34 (19.94-28.73)
- Female	534	3640	38	7%	10.44 (7.12-13.76)
Age group					
- 40~49 years old	159	1102	9	6%	8.17 (2.83-13.51)
- 50~59 years old	233	1591	19	8%	11.94 (6.57-17.31)
- 60~69 years old	399	2626	57	14%	21.70 (16.07-27.34)
- 70~79 years old	365	2337	60	16%	25.67 (19.18-32.17)
- 80 years old or	124	833	11	9%	13.21 (5.40-21.02)

more					
Smoking (%)					
- never smoker	678	4522	77	11%	17.03 (13.23-20.83)
- previous or current smoker	320	2093	48	15%	22.93 (16.44-29.42)
- unknown	282	1771	45	16%	25.41(17.99-32.84)
Income level					
- 0-3	391	2606	41	10%	15.73 (10.92-10.55)
- 4~7	346	2268	48	14%	21.16 (15.17-27.15)
- 8~10	543	3615	67	12%	18.54 (14.10-22.97)
Co-morbidities known to be associated with exacerbation					
- Atrial fibrillation	10	63	1	10%	15.92 (-15.28-47.12)
- GERD	75	488	6	8%	12.29 (2.26-22.12)
- Pneumonia	37	221	7	19%	31.67 (8.21-55.14)
- Heart Failure	38	245	6	16%	24.48 (4.89-44.08)
- Thrombo-embolism	1	7	0	0%	0.00
- Depression	27	184	1	4%	5.43 (-5.22-16.08)
- Bronchitis	87	587	11	13%	18.74 (7.67-29.82)

Severity at diagnosis					
- Mild	685	4625	59	9%	12.76 (9.50-16.01)
- Moderate	383	2536	47	12%	18.53(13.24-23.83)
- Severe	212	1329	50	24%	37.63 (27.20-48.06)

* Incidence proportion(IP)= event/total

**p-y= person-year

3.3.3 Incidence rate of acute exacerbation for different severities of COPD at diagnosis

When incidence rate of acute exacerbation was analysed for different severities of COPD at diagnosis, female patients showed increasing trend of incidence rate as the severities of COPD at diagnosis increased. Also the incident rates were higher than male patients other than for patients diagnosed as mild COPD and the highest incidence rate of acute exacerbation was observed with female patients with severe COPD at diagnosis which the rate was 30.94 per 1,000 person-year (95% CI: 14.12-47.76).

The incidence rate of acute exacerbation was higher in the previous or current smoking patients compared to never smoker patients at all severity.

For all age groups, incidence rate of acute exacerbation was the highest for patients diagnosed as severe COPD. The highest incidence rate was observed with 50~59 years old patients with severe COPD at diagnosis iwhich the incidence rate of acute exacerbation was 35.88 per 1,000 person-year (95% CI: 11.02-60.75). On the other had the lowest incidence rate was observed with patients diagnosed as mild COPD in 50~59 years old patient group which the incidence rate of acute exacerbation was 1.18 per 1,000 person-year (95% CI: -1.13-3.48) however the 95% confidence interval includes negative value.

There was no specific trend of incidence rate observed for patients with different income level, and the highest incidence rate of acute exacerbation was observed for patients with severe COPD at diagnosis in level 8~10 patients which the rate was 32.29 per 1,000 person-year (95% CI: 16.94-47.65).

There was also no specific trend of incidence rate observed for patients with different co-morbidities known to be associated with acute exacerbation, and the highest incidence rate of acute exacerbation which the 95% confidence interval did not include negative value was observed for severe COPD patients with bronchitis which the rate was 59.90 per 1,000 person-year (95% CI: 97-107.83).

Table 6. Incidence rate of acute exacerbation for different severities of COPD at diagnosis

	Severity at diagnosis of COPD		
	Mild	Moderate	Severe
	Incidence per 1,000 p-y	Incidence per 1,000 p-y	Incidence per 1,000 p-y
Sex			
- Male	11.04 (6.88-15.21)	8.82 (4.20-13.44)	20.24 (10.89-29.59)
- Female	10.46 (6.09-14.83)	13.58 (6.20-20.96)	30.94 (14.12-47.76)
Age group			
- 40~49 years old	7.79 (0.96-14.62)	17.81 (2.20-33.43)	32.49 (0.65-64.33)
- 50~59 years old	1.18 (-1.13-3.48)	10.33 (1.28-19.39)	35.88 (11.02-60.75)
- 60~69 years old	13.94 (7.67-20.20)	7.77 (1.55-14.00)	28.80 (13.14-44.45)
- 70~79 years old	12.27 (6.06-18.48)	12.59 (4.79-20.39)	13.08 (1.62-24.55)
- 80 years old or more	5.84 (-0.77-12.45)	4.66 (-4.48-13.80)	7.70 (-7.39-22.80)
Smoking (%)			
- nevere smoker	17,10(11.93-22.27)	13.44 (7.05-19.82)	34.90 (19.61-50.20)
- previous or current smoker	18.54 (9.97-27.10)	20.40 (9.31-31.49)	42.16 (20.83-63.50)

- unknown	5.98 (1.20-10.77)	18.13 (6.89-29.37)	26.91 (8.26-45.56)
Income level			
- 0-3	10.33 (5.10-15.56)	7.48 (1.49-13.46)	19.99 (5.18-34.79)
- 4~7	11.02 (5.03-17.01)	20.46 (9.34-31.58)	16.17 (4.19-28.15)
- 8~10	7.65 (3.78-11.52)	7.23 (2.22-12.23)	32.29 (16.94-47.65)
Co-morbidities known to be associated with exacerbation			
- Atrial fibrillation	61.56 (-59.10-182.22)	-	-
- GERD	3.71 (-3.56-10.98)	5.45 (-5.23-16.14)	-
- Pneumonia	10.83 (-10.40-32.06)	10.49 (-10.07-31.04)	-
- Heart Failure	23.59 -3.10-50.29)	12.27 (-11.78-36.31)	-
- Thrombo-embolism	-	-	-
- Depression	-	-	-
- Bronchitis	6.73 (-2.60-16.06)	12.14 -4.69-28.97)	59.90 11.97-107.83)

3.3.4 Incidence rate of severe acute exacerbation for different severities of COPD at diagnosis

When incidence rate of severe acute exacerbation was analysed for different severities of COPD at diagnosis, the both male and female patients showed increasing trend of incidence rate as the severities of COPD at diagnosis increased. Also the incident rates were higher for male patients compared to female patients for all COPD severity groups and the highest incidence rate of severe acute exacerbation was observed with female patients diagnosed as severe COPD which the rate was 46.50 per 1,000 person-year (95% CI: 32.09-60.92).

For all age groups except 40~49 years old group, incidence rate of severe acute exacerbation was the highest with patients diagnosed as severe COPD. The highest incidence rate was observed with severe COPD patients in 60-69 years old patient group which the incidence rate of severe acute exacerbation was 49.35 per 1,000 person-year (95% CI: 29.18-69.53).

The incidence rate of severe acute exacerbation was higher in the previous or current smoking patients compared to never smoker patients at all severity.

For different income levels except level 0~3 the incidence rate of

severe acute exacerbation showed increasing trend of as the severities of COPD at diagnosis increased, and the highest incidence rate of severe acute exacerbation was observed for patients in level 0~3 who were diagnosed with severe COPD which the rate was 42.26 per 1,000 person-year (95% CI: 20.12-64.40).

There was also no specific trend of incidence rate observed for patients with different co-morbidities known to be associated with severe acute exacerbation, and the highest incidence rate of severe acute exacerbation was observed for pneumonia patients diagnosed as severe COPD which the rate was 117.29 per 1,000 person-year (95% CI: 2.35-232.23).

Table 7. Incidence rate of severe acute exacerbation for different severities of COPD at diagnosis

	Severity at diagnosis of COPD		
	Mild	Moderate	Severe
	Incidence per 1,000 p-y	Incidence per 1,000 p-y	Incidence per 1,000 p-y
Sex			
- Male	17.19 (11.99-21.38)	23.30 (15.69-30.91)	46.50 (32.09-60.92)
- Female	7.80 (4.09-11.50)	11.10 4.54-17.66)	21.34 (8.12-34.57)
Age group			
- 40~49 years old	3.00 (-1.16-7.15)	17.49 (2.16-32.81)	13.49 (-5.21-32.19)
- 50~59 years old	4.69 (0.09-9.28)	18.69 (6.48-30.90)	23.42 (4.68-42.16)
- 60~69 years old	16.61 (9.82-23.40)	14.19 (5.80-22.57)	49.35 (29.18-69.53)
- 70~79 years old	19.63 (11.78-27.49)	25.79 (14.49-37.10)	47.18 (24.06-70.30)
- 80 years old or more	12.09 (2.42-21.77)	9.19 (-3.55-21.92)	25.19 (-3.31-53.69)
Smoking (%)			
- nevere smoker	10.64 (6.70-14.59)	18.66 (11.19-26.13)	41.23 (25.13-57.53)
- previous or current smoker	16.53 (8.67-24.39)	19.28 (8.80-29.77)	46.03 (24.76-67.29)

- unknown	21.72 (12.20-31.24)	27.82 (13.74-41.91)	32.17 (12.23-52.11)
Income level			
- 0-3	13.66 (7.67-19.64)	8.64 (2.24-15.04)	42.26 (20.12-64.40)
- 4~7	14.23 (7.47-21.00)	26.43 (13.87-39.00)	32.49 (15.47-49.51)
- 8~10	11.19 (6.51-15.87)	21.25 (12.56-29.93)	38.84 (22.61-55.07)
Co-morbidities known to be associated with acute exacerbation			
- Atrial fibrillation	-	-	68.91 (-66.15-203.96)
- GERD	7.42 (-2.86-17.70)	17.53 (-2.31-37.36)	21.00 (-20.16-62.17)
- Pneumonia	23.20 (-8.95-55.35)	9.93 (-9.53-29.40)	117.29 (2.35-232.23)
- Heart Failure	31.46 (0.63-62.28)	12.19 (-11.70-36.07)	27.91 (-26.80-82.62)
- Thrombo-embolism	-	-	-
- Depression	-	17.12 (-16.43-50.67)	-
- Bronchitis	13.56 (0.27-26.85)	17.72 (-2.33-37.77)	32.60 (0.65-64.55)

3.4 Number of days to first acute exacerbation

The number of days to first acute exacerbation showed decreasing trend as the severity of COPD at diagnosed increased from mild, moderate to severe which were 423, 315, 297 days respectively.

Table 8. Number of days to first acute exacerbation

	Number of days to first acute exacerbation		
	Mild	moderate	Severe
Median (CI 95%)	423(182-750)	315 (140-473)	297 (149-403)

3.5 Risk of acute exacerbation for different severities of COPD at diagnosis

- Confirmation of proportional hazard assumption

In order to confirm the proportional hazard assumption log minus log graph was generated which has strata of different severities of COPD at diagnosis and as shown in below Figure 9. the cross-over between the different groups were minimal.

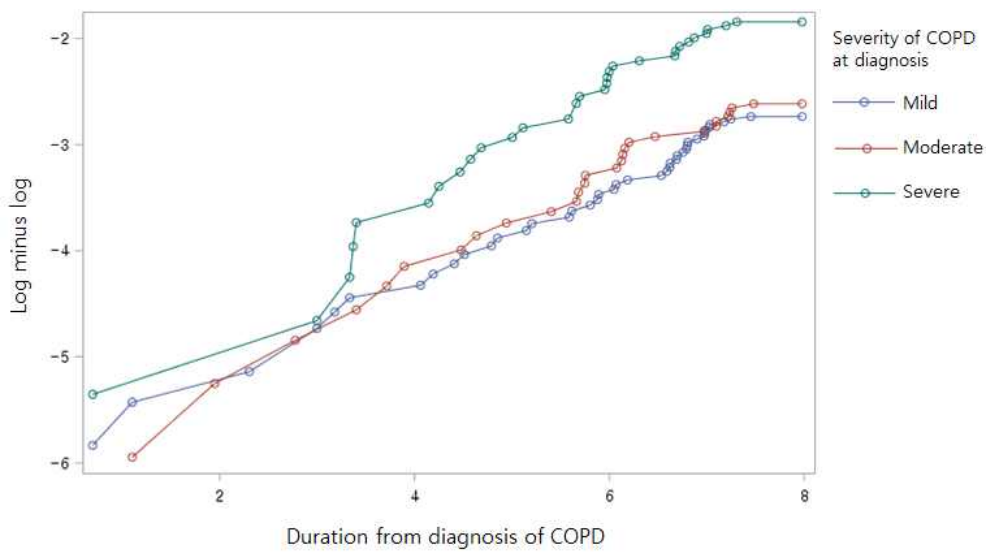

Figure 9. log minus log graph to confirm the proportional hazard assumption between the different severities of COPD at diagnosis

Also, the proportional hazards is that the ratio of hazards is a constant that does not depend on time. When this assumption fails, it is because the hazard ratio changes over time. Therefore to test this assumption, “severity*time to acute exacerbation” interaction was tested and as this interaction term was not significant, the null hypothesis that the hazards are proportional cannot be rejected which means that there is no evidence against proportional hazards.

Table 9. Proportional hazard assumption test for acute exacerbation

	Pr>ChiSq
severity*time to acute exacerbation	0.9376

- Risk of acute exacerbation for different severities of COPD at diagnosis

The risk of acute exacerbation was calculated using the patients diagnosed as mild COPD as a reference.

When compared to mild COPD patients the risk of acute exacerbation was higher for both patients diagnosed as moderate and severe COPD and the risk was almost double for severe COPD patients. However the risk of acute exacerbation was only statistically

significant for patients diagnosed as severe COPD (unadjusted HR: 2.45, 95% CI: 1.54-3.88; adjusted HR: 2.12, 95% CI: 1.43-3.14).

For both male and female patients, the risk of acute exacerbation was higher for patients diagnosed as moderate or severe COPD patients although male patients diagnosed as moderate COPD showed lower risk compared to patients diagnosed as mild COPD but it was not statistically significant. Also female patients showed higher risk of acute exacerbation compared to male patients for both moderate and severe COPD patients and the risk was only statistically significant for female patients who had severe COPD at diagnosis(unadjusted HR: 3.93, 95% CI: 1.89-8.17; adjusted HR: 4.47, 95% CI: 2.40-8.35).

Both previous or current smoker showed numerically higher increase in risk of acute exacerbation compared to never smoker patients

Patient diagnosed as severe COPD had higher risk of acute exacerbation compared to moderate COPD patients for all age groups. The highest risk of acute exacerbation was 50~59 year old patients who were diagnosed as severe COPD (unadjusted HR: 27.63, 95% CI: 3.46-220.94; adjusted HR: 5.50 95% CI: 2.00-15.11).

The only statistically significant risk of acute exacerbation for different income levels was level 8~10 patients who had severe COPD

at diagnosis (unadjusted HR: 4.04, 95% CI: 2.02-8.09; adjusted HR: 3.83, 95% CI: 2.14-6.86)

For co-morbidities known to be associated with acute exacerbation, the only statistically significant risk of acute exacerbation patients with bronchitis who had severe COPD at diagnosis (unadjusted HR: 7.73, 95% CI: 1.56-38.35; adjusted HR: 5.87, 95% CI: 1.56-22.11).

Table 10. Risk of acute exacerbation for different severities of COPD at diagnosis

	Unadjusted HR			Adjusted HR		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total	Ref.	1.13 (0.70-1.82)	2.45 (1.54-3.88)	Ref.	1.07 (0.72-1.59)	2.12 (1.43-3.14)
Sex						
- Male	Ref.	0.81 (0.42-1.54)	1.79 (0.99-3.26)	Ref.	0.81 (0.49-1.34)	1.35 (0.81-2.29)
- Female	Ref.	1.78 (0.86-3.70)	3.93 (1.89-8.17)	Ref.	1.68 (0.88-3.22)	4.47 (2.40-8.35)
Age group						
- 40~49	Ref.	2.25	4.18	Ref.	2.40	2.26

years old		(0.65-7.78)	(1.12-15.58)		(0.92-6.21) (0.69-7.37)
- 50~59 years old	Ref.	8.46 (0.99-72.38)	27.63 (3.46-220.94)	Ref.	2.52 5.50 (0.86-7.35) (2.00-15.11)
- 60~69 years old	Ref.	0.57 (0.23-1.42)	1.97 (0.97-3.98)	Ref.	0.58 1.77 (0.27-1.26) (0.92-3.38)
- 70~79 years old	Ref.	1.03 (0.46-2.29)	1.07 (0.39-2.93)	Ref.	1.02 1.57 (0.50-2.06) (0.72-3.44)
- 80 years old or more	Ref.	0.81 (0.08-7.74)	1.35 (0.14-12.93)	Ref.	0.99 0.84 (0.19-5.16) (0.09-7.92)
Smoking (%)					
- never smoker	Ref.	0.79 (0.45-1.38)	1.92 (1.13-3.23)	Ref.	0.86 2.05 (0.49-1.52) (1.19-3.53)
- previous or current smoker	Ref.	1.09 (0.54-2.24)	2.12 (1.07-4.21)	Ref.	1.05 2.07 (0.50-2.20) (1.01-4.25)
- unknown	Ref.	2.98 (1.08-8.21)	4.32 (1.50-12.44)	Ref.	2.65 2.98 (0.94-7.42) (1.00-8.81)
Income level					
- 0-3	Ref.	0.73 (0.28-1.87)	1.89 (0.77-4.64)	Ref.	0.71 1.78 (0.34-1.50) (0.86-3.69)

- 4~7	Ref.	1.79 (0.83-3.86)	1.43 (0.57-3.59)	Ref.	1.44 (0.71-2.89)	1.01 (0.43-2.41)
- 8~10	Ref.	0.95 (0.40-2.24)	4.04 (2.02-8.09)	Ref.	1.30 (0.67-2.51)	3.83 (2.14-6.86)
Co-morbidities known to be associated with exacerbation						
- Atrial fibrillation	Ref.	-	-	Ref.	-	-
- GERD	Ref.	1.46 (0.09-23.39)	-	Ref.	3.76 (0.12-113.8)	21.08 (0.33-1362)
- Pneumonia	Ref.	1.04 (0.065-16.56)	-	Ref.	-	-
- Heart Failure	Ref.	0.51 (0.053-4.93)	-	Ref.	0.63 (0.045-8.96)	-
- Thrombo-embolism	Ref.	-	-	Ref.	-	-
- Depression	Ref.	-	-	Ref.	-	-
- Bronchitis	Ref.	1.77 (0.25-12.60)	7.73 (1.56-38.35)	Ref.	0.80 (0.14-4.61)	5.87 (1.56-22.11)

* multivariate adjustment for sex, age group, smoking, income level, and co-morbidities known to be associated with exacerbation

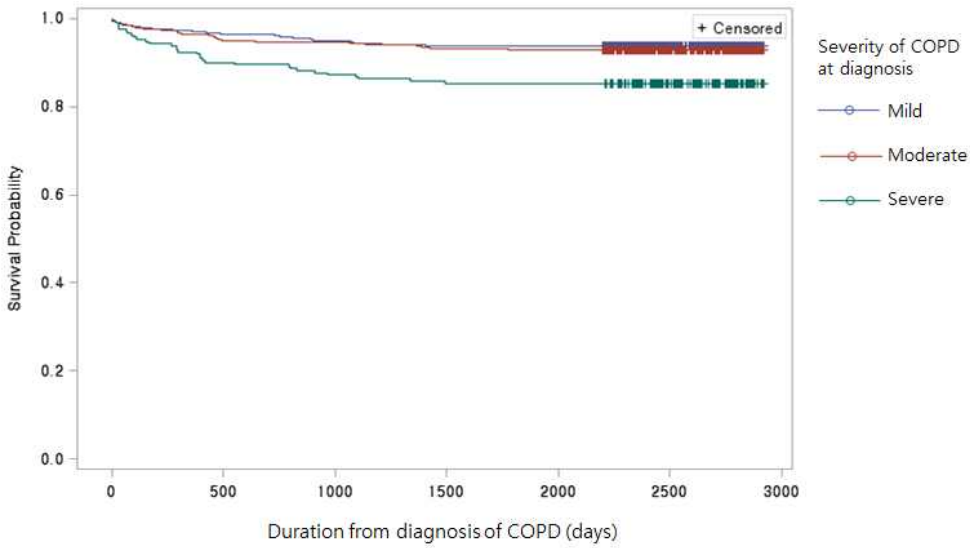

Figure 10. Kaplan-meier curve for risk of acute exacerbation between the different severities of COPD at diagnosis

3.6 Number of days to first severe acute exacerbation

The number of days to first severe acute exacerbation were the shortest for patients diagnosed as moderate COPD, 1,383 days and the longest for patients diagnosed as severe COPD 1,627 days.

Table 11. Number of days to first severe acute exacerbation

	Number of days to first acute exacerbation		
	Mild	moderate	Severe
Median (CI 95%)	1476 (945-1680)	1383 (1106-1688)	1627 (1250-1782)

3.7 Risk of severe acute exacerbation for different severities of COPD at diagnosis

- Confirmation of proportional hazard assumption

In order to confirm the proportional hazard assumption log minus log graph was generated which has strata of different severities of COPD at diagnosis and as shown in below Figure 9. there was one cross-over between mild and moderate groups.

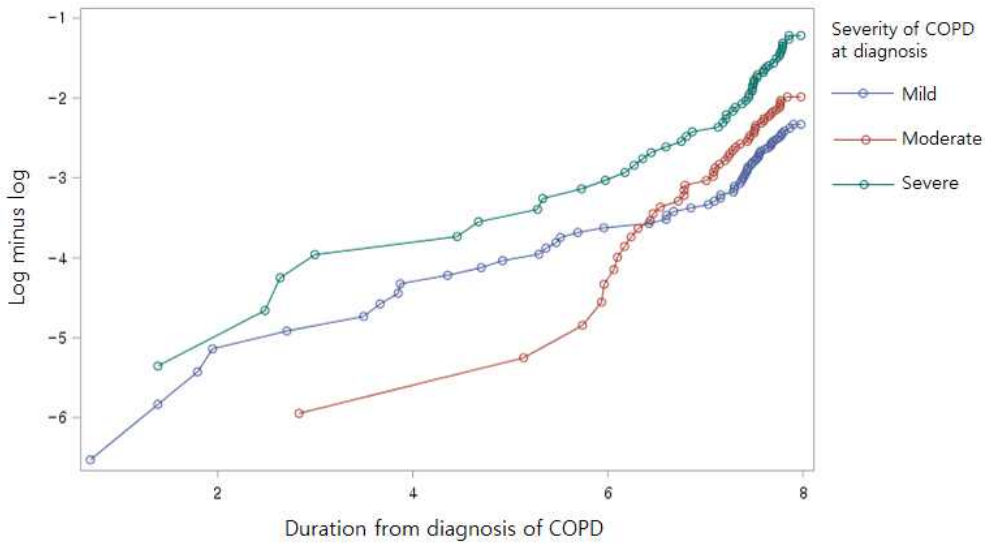

Figure 11. log minus log graph to confirm the proportional hazard assumption between the different severities of COPD at diagnosis

Same as for risk of acute exacerbation, “severity*time to severe acute exacerbation” interaction was tested and as this interaction term was also not significant, the null hypothesis that the hazards are proportional cannot be rejected which means that there is no evidence against proportional hazards.

Table 12. Proportional hazard assumption test for severe acute exacerbation

	Pr>ChiSq
severity*time to severe acute exacerbation	0.1658

- Risk of severe acute exacerbation for different severities of COPD at diagnosis

The risk of severe acute exacerbation was calculated using patients diagnosed as mild COPD as a reference.

When compared to patients diagnosed as mild COPD the risk of severe acute exacerbation was higher for both patients diagnosed as moderate and severe COPD and the risk was almost double for

severe COPD patients. The risk of severe acute exacerbation for was only statistically significant for patients diagnosed as severe COPD (severe COPD at diagnosis; unadjusted HR: 2.94, 95% CI: 2.02-4.29; adjusted HR: 2.56, 95% CI: 1.77-3.71).

For both male and female patients, the risk of severe acute exacerbation was higher for patients diagnosed as severe COPD than moderate COPD.

Patients diagnosed as severe COPD had higher risk of severe acute exacerbation compared to patients diagnosed as moderate COPD for all age groups except for 40~49 years old group. The highest risk of severe acute exacerbation was 40~49 year old patients who were diagnosed as moderate COPD (unadjusted HR: 5.98, 95% CI: 1.16-30.85; adjusted HR: 5.84, 95% CI: 1.03-33.21).

Both never smoker and previous or current smokers showed higher risk of severe acute exacerbation for patients with moderate and severe COPD at diagnosis compared to mild COPD patients. Also never smoker patients showed numerically higher increase in risk compared to previous or current smoker patients.

The risk of severe acute exacerbation was higher for patients diagnosed as severe COPD compared to moderate COPD patients for all income level. The highest risk of severe acute exacerbation was

level 8~10 patients who were diagnosed as severe COPD (unadjusted HR: 3.49, 95% CI: 1.93-6.31; adjusted HR: 3.51, 95% CI: 1.97-6.25).

For co-morbidities known to be associated with severe acute exacerbation, the highest risk of severe acute exacerbation was with patients with heart failure diagnosed as severe COPD when the risk was adjusted (adjusted HR: 12.73, 95% CI: 1.41-115).

Table 13 Risk of severe acute exacerbation for different severities of COPD at diagnosis

	Unadjusted HR			Adjusted HR		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total	Ref.	1.45 (0.99-2.13)	2.94 (2.02-4.29)	Ref.	1.36 (0.94-1.96)	2.56 (1.77-3.71)
Sex						
- Male	Ref.	1.35 (0.87-2.11)	2.706 (1.75-4.17)	Ref.	1.34 (0.87-2.08)	2.59 (1.68-3.40)
- Female	Ref.	1.42 (0.67-3.03)	2.714 (1.24-5.93)	Ref.	1.54 (0.77-3.06)	2.48 (1.18-5.24)
Age group						
- 40~49	Ref.	5.98	4.48	Ref.	5.84	7.89

years old		(1.16-30.85)	(0.63-31.82)		(1.03-33.21) (0.92-67.40)
- 50~59 years old	Ref.	4.07 (1.25-13.20)	5.10 (1.44-18.09)	Ref.	4.45 3.45 (1.35-14.68) (0.95-12.53)
- 60~69 years old	Ref.	0.86 (0.42-1.76)	3.01 (1.69-5.37)	Ref.	0.75 2.09 (0.37-1.51) (1.15-3.81)
- 70~79 years old	Ref.	1.31 (0.72-2.36)	2.36 (1.25-4.44)	Ref.	1.52 2.50 (0.85-2.71) (1.31-4.79)
- 80 years old or more	Ref.	0.76 (0.15-3.75)	2.06 (0.52-8.25)	Ref.	0.32 2.36 (0.06-1.61) (0.74-7.54)
Smoking (%)					
- never smoker	Ref.	1.76 (1.02-3.03)	3.88 (2.26-6.65)	Ref.	1.73 3.58 (0.98-3.03) (2.02-6.33)
- previous or current smoker	Ref.	1.17 (0.57-2.41)	2.80 (1.44-5.42)	Ref.	1.08 2.70 (0.51-2.27) (1.37-5.33)
- unknown	Ref.	1.28 (0.67-2.51)	1.46 (0.68-3.12)	Ref.	1.33 1.48 (0.67-2.64) (0.67-3.26)
Income level					
- 0-3	Ref.	0.64 (0.27-1.50)	3.05 (1.54-6.04)	Ref.	0.48 2.30 (0.21-1.12) (1.14-4.63)

- 4~7	Ref.	1.84 (0.94-3.60)	2.24 (1.10-4.54)	Ref.	1.64 (0.84-3.17)	2.04 (1.01-4.11)
- 8~10	Ref.	1.90 (1.06-3.41)	3.49 (1.93-6.31)	Ref.	1.95 (1.11-3.41)	3.51 (1.97-6.25)
Co-morbidities known to be associated with exacerbation						
- Atrial fibrillation	Ref.	-	-	Ref.	-	-
- GERD	Ref.	2.31 (0.37-13.82)	2.70 (0.24-29.75)	Ref.	10.8 0.77-152)	9.82 (0.33-294)
- Pneumonia	Ref.	0.46 (0.042-5.09)	4.55 (0.83-24.87)	Ref.	0.06 (0.001-2.12)	3.80 (0.19-76.6)
- Heart Failure	Ref.	0.41 (0.046-3.67)	0.91 (0.10-8.15)	Ref.	0.68 (0.042-10.9)	12.73 (1.41-115)
- Thrombo-embolism	Ref.	-	-	Ref.	-	-
- Depression	Ref.	-	-	Ref.	-	-
- Bronchitis	Ref.	1.28 (0.29-5.73)	2.40 (0.60-9.61)	Ref.	0.90 (0.19-4.28)	2.13 (0.50-9.02)

* multivariate adjustment for sex, age group, smoking, income level, and co-morbidities known to be associated with exacerbation

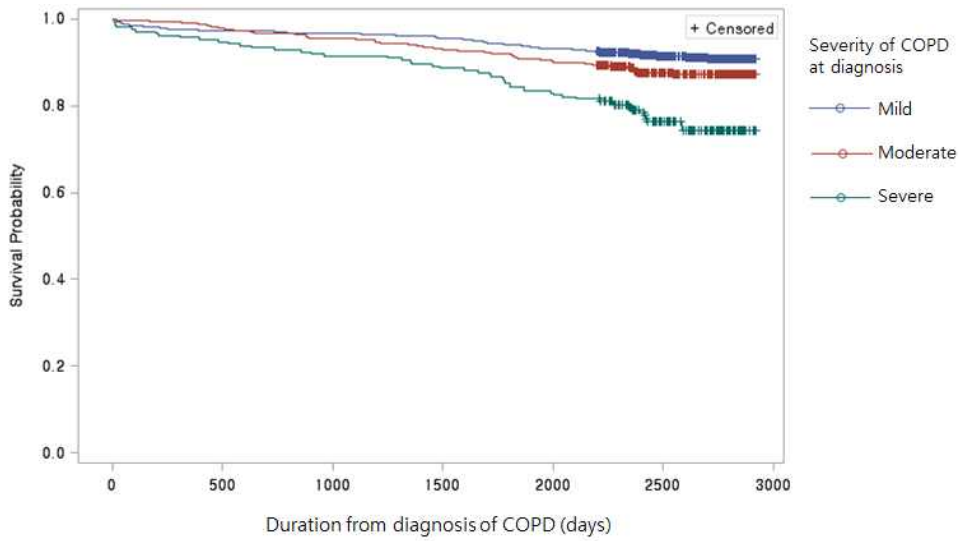

Figure 12. Kaplan-meier curve for risk of severe acute exacerbation between the different severities of COPD at diagnosis

3.8 Sensitivity analysis

Sensitivity analysis was carried out in order to assess the possible misclassification of COPD patients and misclassification of baseline severity in various ways and compared it with the baseline analysis to assess the possible impacts of these variables on the result.

For all sensitivity analysis, general trend of result was similar to baseline analysis (Table 14, 15, 16).

Table 14. Sensitivity analysis result of excluding never-smokers: risk of acute exacerbation and severe acute exacerbation

	Unadjusted risk of acute exacerbation: HR (95% CI)			Adjusted risk of acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total n=602	Ref.	1.57 (0.89-2.79)	2.72 (1.54-4.83)	Ref.	1.50 (0.84-2.67)	2.40 (1.35-4.30)
	Unadjusted risk of severe acute exacerbation: HR (95% CI)			Adjusted risk of severe acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total n=602	Ref.	1.21 (0.74-1.98)	2.08 (1.27-3.39)	Ref.	1.24 (0.75-2.03)	2.09 (1.26-3.45)

* multivariate adjustment for sex, age group, smoking, income level, and co-morbidities known to be associated with exacerbation

* HR= Hazard ratio

Table 15. Sensitivity analysis result of more strict COPD diagnosis criteria: risk of acute exacerbation and severe acute exacerbation

COPD prescriptions/year	Unadjusted risk of acute exacerbation: HR (95% CI)			Adjusted risk of acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
≥3 (n=261)	Ref.	1.42 (1.06-1.91)	1.45 (1.02-2.06)	Ref.	1.48 (1.01-1.99)	1.48 (1.03-2.13)
≥4 (n=310)	Ref.	1.57 (1.09-2.25)	1.35 (0.86-2.14)	Ref.	1.69 (1.16-2.48)	1.43 (0.88-2.32)
≥2 and ≥30day duration (n=275)	Ref.	2.68 (1.56-4.62)	2.50 (1.39-4.51)	Ref.	2.50 (1.44-4.33)	2.23 (1.26-4.10)
≥2 and ≥60day	Ref.	1.23 (0.28-5.50)	1.72 (0.40-7.67)	Ref.	0.15 (0.02-0.88)	0.15 (0.02-0.99)

duration (n=101)						
COPD prescriptions/year	Unadjusted risk of severe acute exacerbation: HR (95% CI)			Adjusted risk of severe acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
≥3 (n=261)	Ref.	1.32 (1.00-1.74)	2.78 (1.71-3.04)	Ref.	1.27 (0.96-1.68)	2.16 (1.58-2.96)
≥4 (n=310)	Ref.	1.44 (1.02-2.02)	2.25 (1.56-3.26)	Ref.	1.35 (0.95-1.92)	2.15 (1.41-3.26)
≥2 and ≥30day duration (n=275)	Ref.	2.14 (1.37-3.35)	2.66 (1.67-4.24)	Ref.	2.17 (1.37-3.43)	2.27 (1.39-3.71)
≥2 and ≥60day duration (n=101)	Ref.	2.06 (0.48-8.88)	2.34 (0.54-10.24)	Ref.	0.83 (0.17-3.85)	0.85 (0.17-4.16)

* multivariate adjustment for sex, age group, smoking, income level, and co-morbidities known to be associated with exacerbation

* HR= Hazard ratio

Table 16. Sensitivity analysis result of excluding “no COPD prescriptions for follow-up year 1, 3, 5”: risk of acute exacerbation and severe acute exacerbation

	Unadjusted risk of acute exacerbation: HR (95% CI)			Adjusted risk of acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total n=843	Ref.	0.97 (0.65-1.45)	1.70 (1.15-2.52)	Ref.	0.98 (0.66-1.46)	1.69 (1.13-2.54)
	Unadjusted risk of severe acute exacerbation: HR (95% CI)			Adjusted risk of severe acute exacerbation: HR (95% CI)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Total n=843	Ref.	1.42 (0.96-2.10)	2.54 (1.76-3.74)	Ref.	1.32 (0.89-1.96)	2.30 (1.55-3.42)

* multivariate adjustment for sex, age group, smoking, income level, and co-morbidities known to be associated with exacerbation

* HR= Hazard ratio

4. Discussion

This prospective cohort study was carried out using the National Health Insurance Service- National Sample Cohort(NHIS-NSC) and aimed to analyse the risk of acute exacerbation and severe acute exacerbation between the patients diagnosed as different severities of COPD, which were mild, moderate and severe COPD.

From the baseline characteristics analysis, male patients, 60~69 years old and 70~79 years old patients, level 8~10 income level patients, bronchitis and gastro-oesophageal reflux disease showed high proportion amongst all severities of COPD at diagnosis. They are known factors associated with COPD which the prevalence of COPD in men are higher than women as there are more male tobacco smokers compared to female smokers and smoking is one of the most critical attributing factor of COPD(15). COPD is widely recognised age-related disease and the local data reported highest prevalence of COPD in 60~70 year old patients(3). Also the reason for higher prevalence in 60s and 70s compared to 80 year old or more patients may be due to the "healthy survivor" effect which is higher mortality of patients before they reach their 80s so only the few "healthy

survivors" remain(17). Lower socio-economic status is associated with an increased risk of developing COPD which correlates with our study result where lowest income level group had the highest proportion of COPD(18). COPD often coexists with other diseases that may have a significant impact on prognosis which includes pneumonia and gastro-oesophageal reflux disease which also are independent risk factor for acute exacerbation associated with resulting in worse health outcome(1).

It was shown from our study that incidence rate per 1000 person year for acute exacerbation and severe acute exacerbation increased as the severity of COPD increased from mild, moderate to severe which the increase was greater for incidence rate of severe acute exacerbation (incidence rate of severe acute exacerbation for mild, moderate, severe COPD at diagnosis; 9%, 12%, 24%). Although the classification of severity of COPD from our study was not based on spirometric result, it was reported that there is a significant relationship between spirometric severity and the risk of acute exacerbation and death. The patients classified as GOLD 2 (moderate severity) may experience frequent acute exacerbation(12) and the risk of acute exacerbation is significantly higher for GOLD 3 (severe) and GOLD 4 (very severe) patients(20).

Male patients demonstrated more than double incidence rate of severe COPD acute exacerbation compared to female patients. Previous local study reported newly diagnosed COPD patients visiting emergency room (ER) and recurrent ER visit was higher for male compared to female patients (adjusted OR of ER visit and recurrent ER visit with female patients as a reference: 1.48, 1.42)(21). However there are also recent studies reporting higher rate of acute exacerbation in female patients compared to male patients suggesting that females maybe more prone to have severe acute exacerbation and that women develop severe COPD at younger ages and with less cumulative cigarette smoke(12)(22).

When incident rates of acute exacerbation and severe acute exacerbation were analysed for different severities of COPD at diagnosed (Table 6, Table 7), for all domains of patient characteristics except co-morbidities known to be associated with acute exacerbation, incidence rates increased as the severity the severity of COPD at diagnosis increase especially for severe COPD at diagnosis. This result demonstrates that regardless of patient characteristics, incidence of acute exacerbation and severe acute exacerbation increases as the severity of COPD at diagnosis increases and especially for severe COPD at diagnosis.

As for the number of days to first acute exacerbation there was a decreasing trend of days to first acute exacerbation as the severity of COPD at diagnosis increased. This means that patients diagnosed with more severe COPD experience acute exacerbation within shorter period of time, compared to patients diagnosed with less severe COPD.

When compared to patients diagnosed as mild COPD, the risk of acute exacerbation and severe acute exacerbation was higher for patients diagnosed as moderate and severe COPD. Although both the patients diagnosed as moderate and severe COPD showed increased risk of acute exacerbation and severe acute exacerbation compared to patient diagnosed as mild COPD, the increased risk was only statistically significant for patients diagnosed as severe COPD. This correlates with the previous study data which reported odds ratio of acute exacerbation per increase to next GOLD stage was 1.74 ($p<0.001$), which means as the severity by GOLD stage increases, the rate of acute exacerbation also increases(12). However interestingly the local study, Kim et al(21), which analysed the effect of inhaled long-acting bronchodilator compared to short-acting bronchodilator in newly-diagnosed COPD patients, patients with short-acting bronchodilator showed more emergency room(ER) visits, recurrent ER

visits, hospitalisation, and recurrent hospitalisation when compared to long-acting bronchodilator patients. The difference between result of our study and Kim et al may largely be due to difference in follow-up period which the follow-up was 1 year for Kim et al, and 6~7 years for our study. Our study also showed more acute exacerbation and severe acute exacerbation events in patients diagnosed as mild COPD compared to patients diagnosed as moderate COPD in earlier stage of follow-up which was reversed in later stage of follow-up (Figure 10-13). This may mean that there could have been portion of patients diagnosed as mild COPD patients who were prescribed with short-acting agents but in fact should have been treated with more aggressive treatments or these mild COPD patients may have portion of patients who are non-compliant to the medication due to their mild symptoms therefore experienced acute exacerbation or severe acute exacerbation earlier than they should have.

Female patients, patients in their 40s and 50s, lowest income level patients(level 8~10), and patients with heart failure and bronchitis diagnosed with moderate or severe COPD demonstrated much higher risk of acute exacerbation or severe acute exacerbation as compared to patients diagnosed as mild COPD. In these patients, who showed

greater increase in risk of acute exacerbation or severe acute exacerbation, would specifically need to be monitored closely so they are not diagnosed as late stage of COPD as their prognosis may be worse than the others.

There were some limitations to our study. Firstly as our data source NHIS-NSC is a claims data, there is an inherent risk of misclassification of the patients enrolled to the cohort. This is because the disease codes in the claims data may not represent the true disease status of the patients as the physicians would tend to use the codes that are reimbursable which is also mentioned in the profile study of this cohort database(e.g. COPD code may have been used in order to prescribe COPD medications for bronchitis patients)(11).

Therefore our study used the operational definition of COPD (over 40 years old, prescription of COPD medication at ≥2 separate times and use of ICD-10 diagnostic codes) provided by Lee et al.(13) which is the definition of COPD that is used when analysing the claims data. This criteria was validated by previous local studies(17, 21, 23) as “practical” population of COPD when using the claims data, and also this criteria was found to be similar to the criteria used by other studies using claims datal(25, 26, 27).

However it still carries the inherent limitation of claims data that the claimed disease code may not represent the true disease status of the patients. Therefore sensitivity analysis was carried out to assess the specificity of the COPD diagnosis criteria and the result showed that even if the COPD diagnosis criteria were made more strict, the result has similar trend to the baseline analysis therefore the possible impact of misclassification with COPD diagnosis criteria may be insignificant. However future studies that confirm the result of the current study by using the patient data that is not from the insurance database would be still be necessary.

Secondly our study used treatment patterns of the enrolled patients to define their disease severity however this may have provided potential for misclassification of disease severity of the patients. Traditionally spirometry which measures the lung function was used as a lone method of COPD diagnosis and classification of disease severity. However although FEV1 is an essential parameter at the population level in predicting critical clinical outcomes, it may lose its precision at individual patient level. Also as patient-reported outcomes and acute exacerbation prevention in the management of COPD has become more important, it is now recommended by GOLD guideline that spirometry in conjunction with patient symptoms and acute

exacerbation history remains vital for the diagnosis and classification of disease severity(1).

Our data source did not have Pulmonary Function Test results, therefore we classified patients' severity using their treatment patterns and this may reflect the "real world" more closely as compared to using pulmonary function data alone. However as our study still missed the lung function results to support the treatment decision of the patients, our study still carried the potential for misclassification of disease severity at diagnosis. And out of all misclassified patients, over-prescribed patients especially patients who were not in fact COPD patients are critical as they may bias the study results towards strengthening the study result.

Therefore sensitivity analysis was carried out by excluding the patients who did no have any COPD prescriptions for all 3 years of follow-up year 1, 3 and 5 before the event occurrence(acute exacerbation or severe acute exacerbation). The result showed similar trend to the baseline analysis therefore the possible impact of misclassification of baseline severity especially for over-prescribed patients may be insignificant.

Thirdly the definition of acute exacerbation and severe acute exacerbation was derived from COPD guideline and from previous

studies(1, 12, 24), not from the operational definition developed for the use of claims data. This was because currently there is no locally defined operational definition of COPD acute exacerbation or severe acute exacerbation when using the claims data. And also this criteria was still used as it is more strict criteria compared to previous studies. However it is not a locally validated criteria and there is potential for misclassifying the events of acute exacerbation and severe acute exacerbation in our study such as picking up use of systemic steroids and antibiotics that were used when treating upper respiratory track with the COPD ICD-10 codes. Also, the GOLD guideline defines the mild acute exacerbation as acute exacerbation that is treated with short acting bronchodilators only, so our study may have missed the patients whose acute exacerbation was treated with short acting bronchodilators only.

Lastly, the proportion of never-smoker population in this cohort was unusually high. Smoking is one of the most critical factor related to COPD, but other environmental exposures such as biomass fuel exposures and air pollutions may also contribute. Previous studies reported proportion of never-smokers who were defined as “smoked >20 packs of cigarettes in a lifetime or >1 cigarette/d for a year.” or “smoking >100 cigarettes (five packs) in a lifetime” to be

approximately 30%(30, 31, 32). Previous studies also reported the risk factors of COPD in never smoker as increased age, prior diagnosis of asthma, women, lower education level. However our study showed more than double proportion of never smokers in COPD patients, without significant increase in named risk factors of COPD in never smokers such as high proportion of women, or increased age. This maybe due to misclassification of COPD patients who are not true COPD patients being enrolled to the study or misclassification of never-smokers from the health-examination data who are not true never-smoker.

Also, high proportion of never-smokers may have been due to our study enrolled patients based on their COPD treatments as our data source did not have the lung function test result. This may mean our study reflected more realistic COPD patients than the previous studies who used the lung function test as a lone method of enrolment. This is because the treatment decision used in the COPD patients reflects the consideration of both lung function result and also symptomatic factors of patients.

In addition, proportion of never-smokers in the study can be estimated using the relative risk of developing COPD between smokers and non-smokers. If we take male patients into the

consideration, as most of female patients were never smokers, the previous meta-analysis study(33) reported relative risk of developing COPD in ever-smokers as compared to never-smokers was 2.89, current-smokers as compared to never-smokers was 3.51, and ex-smokers as compared to never-smokers was 2.35. This means, depending on the proportion of current-smokers and ex-smokers in the population of interest, proportion of never-smoker would be approximately 30%. However the proportion of never-smoker was much higher in our study there is potential of misclassification of false-COPD patients being enrolled to the study.

Therefore in order to assess the potential impact of misclassification of false COPD patients being enrolled to the study may have on the study result, the sensitivity analysis was carried out by excluding all never-smokers. The result of the sensitivity analysis was that it was similar to the baseline analysis, therefore the potential impact of misclassification of false COPD patients being enrolled to the study may be insignificant. However, although the sensitivity analysis showed insignificant impact of misclassification of false COPD patients, as the proportion of never-smoker was significantly higher in this study compared to the previous studies, confirmation of the study result using the primary data would be crucial.

5. Conclusion

This prospective cohort study was carried out using the National Health Insurance Service- National Sample Cohort(NHIS-NSC) and aimed to analyse the risk of acute exacerbation and severe acute exacerbation between the patients diagnosed as different severities of COPD, which were mild, moderate and severe COPD.

As a result, not only the incidence proportion and incidence rate of acute exacerbation and severe acute exacerbation increased as the severity of COPD at diagnosed increased, but also the risk of acute exacerbation and severe acute exacerbation increased in patients diagnosed as moderate COPD and more dramatically with patients diagnosed as severe COPD when compared to patients with mild COPD at diagnosis.

Although future studies would be necessary to confirm the result of the current study by using the non-claims data, the result of current study may still contribute as an evidence to enhancing importance of early diagnosis of COPD.

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Appendix 1. List of drugs used to define diagnosis of COPD and the severity of COPD

Class	Active ingredients	Code
SAMA	ipratropium	177101CLQ
SAMA	ipratropium	177103CLQ
SABA / SAMA	ipratropium / albuterol	334800CAE
SABA	clenbuterol	135301ASY
SABA	clenbuterol / ambroxol	264700ASY
SABA	clenbuterol / ambroxol	264800ATB
SABA	fenoterol	157901ATB
SABA	fenoterol	157902CLQ
SABA	procaterol	218302ATB
SABA	procaterol	218304CSI
SABA	salbutamol	225501ATB
SABA	salbutamol	225503ATB
SABA	salbutamol	225503ACR
SABA	salbutamol	225507ACR
SABA	salbutamol	225502CSI

SABA	salbutamol	225506CSI
SABA	salbutamol	225508CSI
SABA	terbutaline	235801ATB
SABA	terbutaline	235830CLQ
LAMA	tiotropium	457301CSI
LAMA	tiotropium	457301CCH
LAMA	tiotropium	503401CSI
LABA / SABA	Orciprenaline	269500ATB
LABA	bambuterol	113601ATB
LABA	bambuterol	113602ASY
LABA	formoterol	163101ASY
LABA	formoterol	163101ATB
LABA	formoterol	163104ASY
LABA	formoterol	163104ATB
LABA	indacaterol	611901CSI
LABA	indacaterol	611902CSI
LABA	tulobuterol	452101CPC
LABA	tulobuterol	452102CPC

LABA	tulobuterol	452103CPC
ICS / LABA	beclometasone / formoterol	502000CSI
ICS / LABA	budesonide / formoterol	441700CSI
ICS / LABA	budesonide / formoterol	453400CSI
ICS / LABA	salmeterol / fluticasone	506400CSI
ICS / LABA	salmeterol / fluticasone	506500CSI
ICS / LABA	salmeterol / fluticasone	506600CSI
ICS / LABA	budesonide / formoterol	391800CSI
ICS / LABA	salmeterol / fluticasone	334700CSI
ICS / LABA	salmeterol / fluticasone	334600CSI
ICS / LABA	salmeterol / fluticasone	334500CSI
ICS	budesonide	119404CSI
ICS	budesonide	119438CAE
ICS	budesonide	119502CSI
ICS	budesonide	119505CSI
ICS	budesonide	119506CSI
ICS	beclometasone	114508CSI
ICS	beclometasone	114509CSI

ICS	beclometasone	114510CSI
ICS	ciclesonide	497101CSI
ICS	ciclesonide	497102CSI
ICS	fluticasone / propionate	162202CSI
ICS	fluticasone / propionate	162203CSS
ICS	fluticasone / propionate	162204CSI
ICS	fluticasone / propionate	162205CSI
ICS	fluticasone / propionate	162206CSS

* Abbreviations: SAMA, Short acting muscarinic antagonist; SABA, Short acting beta agonist; LAMA, Long acting muscarinic antagonist; LABA, Long acting beta agonist; ICS, Inhaled corticosteroids

Appendix 2. List of drugs used to define acute exacerbation: steroids

Class	Active ingredients	Code
OCS	betamethasone	116401ATB
OCS	budesonide	119501CMS
OCS	deflazacort	140801ATB
OCS	dexametasone	141901ATB
OCS	dexametasone	141903ATB
OCS	fludrocortisone	160201ATB
OCS	hydrocortisone	170901ATB
OCS	hydrocortisone	170905ATB
OCS	methylprednisolone	193302ATB
OCS	prednisolone	217001ATB
OCS	triamcinolone	243201ATB
OCS	triamcinolone	243202ATB
OCS	triamcinolone	243203ATB
OCS	betamethasone / chlorpherinamine	296900ATB
steroid injection	betamethasone	116502BIJ

steroid injection	dexametasone	142201BIJ
steroid injection	dexametasone	142202BIJ
steroid injection	hydrocortisone	171201BIJ
steroid injection	hydrocortisone	171202BIJ
steroid injection	methylprednisolone	193501BIJ
steroid injection	methylprednisolone	193502BIJ
steroid injection	methylprednisolone	193601BIJ
steroid injection	methylprednisolone	193602BIJ
steroid injection	methylprednisolone	193603BIJ
steroid injection	methylprednisolone	193604BIJ
steroid injection	methylprednisolone	217302BIJ
steroid injection	triamcinolone	243301BIJ
steroid injection	triamcinolone	243303BIJ
steroid injection	triamcinolone	243305BIJ

* Abbreviations: OCS, oral corticosteroids

Appendix 3. List of drugs used to define acute exacerbation: antibiotics

Class	Active ingredients	Code
amoxicillin	amoxicillin	108101ACH
amoxicillin	amoxicillin	108101ATB
amoxicillin	amoxicillin	108102ASY
amoxicillin	amoxicillin	108103ACH
amoxicillin	amoxicillin	108103ATB
amoxicillin	amoxicillin	108601ACH
amoxicillin	amoxicillin	589302ACH
amoxicillin / clavulanate	amoxicillin / clavulanate	310400ASY
amoxicillin / clavulanate	amoxicillin / clavulanate	310700ATB
amoxicillin / clavulanate	amoxicillin / clavulanate	358500ASY
amoxicillin / clavulanate	amoxicillin / clavulanate	440100ATB
amoxicillin /	amoxicillin / clavulanate	462000ATB

clavulanate		
amoxicillin / clavulanate	amoxicillin / clavulanate	467200ATB
amoxicillin / clavulanate	amoxicillin / clavulanate	467300ATB
amoxicillin / clavulanate	amoxicillin / clavulanate	467400ATB
amoxicillin / clavulanate	amoxicillin / clavulanate	467600ATB
ampicillin	ampicillin	113101ATB
cephalosporin	cefdinir	125901ACH
cephalosporin	cefdinir	125901AGN
cephalosporin	cefpodoxime	127901ATB
cephalosporin	cefpodoxime	127903ASY
cephalosporin	cefprozil	128001ATB
cephalosporin	cefprozil	128002ASY
cephalosporin	cefuroxime	128903ATB
cephalosporin	cefuroxime	129001BIJ
cephalosporin	cefuroxime	129002BIJ

cephalosporin	cefuroxime	129003BIJ
fluoroquinolones	gemifloxacin	442901ATB
fluoroquinolones	levofloxacin	183201ATB
fluoroquinolones	levofloxacin	183202ATB
fluoroquinolones	levofloxacin	183202BIJ
fluoroquinolones	levofloxacin	183203ATB
fluoroquinolones	levofloxacin	183203BIJ
fluoroquinolones	levofloxacin	183205BIJ
fluoroquinolones	moxifloxacin	380301ATB
fluoroquinolones	moxifloxacin	380302BIJ
macrolide	azithromycin	112701ATB
macrolide	azithromycin	112702ASY
macrolide	azithromycin	112731ASY
macrolide	clarithromycin	134901ATB
macrolide	clarithromycin	134903ASY
macrolide	clarithromycin	134904ATB
macrolide	clarithromycin	134904ATR
macrolide	clarithromycin	134905ASY

macrolide	roxithromycin	225301ATB
macrolide	roxithromycin	225302AGN
macrolide	roxithromycin	225302ATB
macrolide	roxithromycin	225304ASS
tetracycline	doxycycline	149501ACH
tetracycline	doxycycline	149501ATB
tetracycline	doxycycline	149701ACH
tetracycline	doxycycline	149701ATB
tetracycline	doxycycline	149702ACH

SUMMARY IN KOREAN

국문 초록

만성 폐쇄성 폐질환 진단 시 중증도에 따른 급성 악화 및 중증 급성 악화 발생위험비교를 위한 코호트 연구

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연구 배경 및 목적: 만성 폐쇄성 폐질환(COPD; Chronic Obstructive Pulmonary Disease)은 전 세계적으로 가장 흔히 발생하는 폐질환으로 미국의 사망원인 4위, 세계 사망원인 5위를 차지하는 등 이환율 및 사망률에 대표적인 요인으로 꼽히고 있다. 이처럼 COPD는 대중의 건강문제에 있어서 그 심각성이 대두되고 있음에도 불구하고 COPD의 유일한 진

단 검사인 폐기능 검사 진행율은 여전히 낮을 뿐만 아니라 증상에 대한 의료진 및 환자의 낮은 인지도로 인해 많은 환자들이 진단되지 않은 상태로 살아가고 있으며, 최근의 연구에서는 질병 초기에 폐기능이 빠르게 악화되는 경향이 확인되었기 때문에 초기에 진단하여 공격적인 치료 및 금연에 대한 노력을 기울이는 것이 중요한 것으로 나타났다. 이처럼 COPD를 조기에 진단하여 관리하는 것이 중요하지만 실제로 진단 시 중증도에 따라 상이한 건강결과가 나타나는지에 대한 자료는 현재 부재한 상태이며 이를 국민건강 보험공단이 제공하는 표본자료를 이용하여 연구하고자 하였다.

연구방법: 본 전향적 코호트 연구는 건강보험공단에서 제공하는 13개년 표본코호트DB를 활용하여 분석하였다. 2006년 및 2007년에 새로이 만성 폐쇄성 폐질환으로 진단된 환자들을 대상으로 하였으며 임상치료 지침을 이용하여 환자들의 진단시 중증도를 구분하였고, 이들의 급성 악화 및 중증 급성 악화 발생을 2013년 12월 31일 까지 관찰하여 중증도간 위험을 비교하였다.

결과: 총 1,280명의 환자 중 685명이 진단 시 COPD 중증도가 경증, 383명이 중등증, 212명이 중증인 것으로 나타났다. 진단 시 경증의 COPD 환자와 비교하였을 때 진단 시 중등증 COPD 환자의 급성 악화 발생위험이 더 높은 것으로 나타났으며 (unadjusted HR: 1.13, 95% CI: 0.70-1.82; adjusted HR: 1.07, 95% CI: 0.72-1.59) 진단 시 중증 COPD 환자에서는 경증의 COPD 환자 대비 급성 악화 발생위험이 더욱 높은

것으로 분석되었다 (unadjusted HR: 2.45, 95% CI: 1.54-3.88; adjusted HR: 2.12, 95% CI: 1.43-3.14). 또한 중증 급성 악화 발생위험의 경우 진단 시 경증 환자와 비교하였을 때 진단 시 중등증 COPD 환자의 중증 급성 악화 발생위험 또한 더 높은 것으로 나타났고 (unadjusted HR: 1.45, 95% CI: 0.99-2.13; adjusted HR: 1.36, 95% CI: 0.94-1.96), 진단 시 중증 COPD 환자에서는 경증의 COPD 환자 대비 중증 급성 악화 발생위험이 더욱 높은 것으로 분석되었다(unadjusted HR: 2.94, 95% CI: 2.02-4.29; adjusted HR: 2.56, 95% CI: 1.77-3.71).

결론: 진단 시 경증 COPD 환자와 비교하였을 때 진단 시 중등증 및 중증 COPD 환자의 급성 악화 및 중증 급성 악화발생이 더 높은 것으로 분석되었으며 본 연구 결과는 국내 조기 검진 및 조기치료의 필요성에 대한 기초자료로 사용될 수 있을 것이라 사료된다.

주요어: 만성 폐쇄성 폐질환, 급성 악화, 중증 급성 악화, 조기 진단, 청구자료, 전향적 코호트

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