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Incidence of Lung Cancer in Chronic Obstructive Pulmonary Disease Patients: Prognostic Factors and Survival Analysis

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ABSTRACT

OBJECTIVE To estimate the incidence of lung cancer in chronic obstructive pulmonary disease (COPD) patients, to identify the associated prognostic factors and to conduct a survival analysis.

METHODS A retrospective cohort study was conducted between 1 June 2017 and 30 November 2020 with continued follow-up for an additional six months at the COPD Clinic of Phrae Hospital. Patients diagnosed with COPD and registered at the COPD Clinic who were age over 40 years and had a normal chest X-ray (CXR) within the previous year were enrolled. Patients diagnosed with or having a history of lung cancer, incomplete annual CXR or a follow-up period of less than six months were excluded.

RESULTS A total of 316 COPD patients who met the inclusion criteria were analyzed. Seven COPD patients were newly diagnosed with lung cancer during the 3.5-year study period. The incidence rate of lung cancer in COPD patients was 0.69% per person-year. Smoking was a significant prognostic factor for lung cancer in the COPD patients. The mortality rate was significantly higher in patients with lung cancer. The mortality rate in COPD patients who developed lung cancer was 24.5% per person-year, higher than the 1.68% per person-year for patients who did not develop lung cancer.

CONCLUSIONS The incidence rate of lung cancer in COPD patients is higher than in the general population and the mortality rate in COPD patients with lung cancer is higher than those without lung cancer. Annual CXR to detect lung cancer should be performed as part of routine lung cancer screening for COPD patients. Because CXR has lower sensitivity than low-dose computed tomography (LDCT) for detecting lung cancer in the early stage, this study found the incidence of lung cancer is slightly lower than previous reports that using LDCT. Moreover, CXR is simple to use, readily available and inexpensive.

KEYWORDS COPD, lung cancer, incidence rate of lung cancer, annual chest x-ray (CXR)

INTRODUCTION

Lung cancer and chronic obstructive pulmonary disease (COPD) are relatively common in clinical practice. Lung cancer and COPD have similar risk factors and share some symptomatology (1-3). A previous study reported that COPD is common in patients with lung cancer; however, the incidence of lung cancer in patients with COPD is still unclear (4).

The most common risk factor for lung cancer and COPD is smoking (2). Smoking is also one of the prognostic factors for lung cancer in COPD patients. The respective risk of developing lung cancer among male and female smokers vs. nonsmokers is 17.2% and 11.6% vs. 1.3% and 1.4%, respectively (5). Pathobiology of lung cancer development involves the molecular aberrations in oncogenes and tumour

suppressor genes (6). Lung cancers normally initiate from the basal epithelial cells. There are two types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (7). NSCLC constitutes about 85% of cases, comprising 40% adenocarcinoma, 30% squamous cell carcinoma, and 5-10% large cell carcinoma. SCLC constitutes about 15% of lung cancer and is made up of smaller, undifferentiated cells that are fast growing and can spread quickly (8). COPD is one of the risk factors for lung carcinoma, especially for squamous cell carcinoma. Smokers with airflow obstruction are five times as likely to have lung cancer than people with normal lung function (9). Young et al. reported that COPD patients have twice the risk for lung cancer than non-COPD patients (10).

A 2019 study estimated the worldwide mean prevalence of COPD at 13.1% (10.2-15.6%; 95%CI) (11). In 2010, the number of COPD patients were estimated to be about 384 million and the global prevalence of COPD was 11.7% (8.4%-15.0%; 95% CI) (12). Annual deaths from COPD were about 3 million (13). The prevalence of COPD is expected to rise in the next 40 years and the annual deaths from COPD and related conditions are predicted to reach more than 5.4 million by 2060 (14,15). The Burden of Obstructive Lung Disease (BOLD) program reported that the overall prevalence of COPD was 10.1%, 11.8% for men and 8.5% for women and the prevalence among the never-smoked was 3-11% (16). The prevalence of COPD in those age over 40 years in 12 public health regions in Thailand (excluding Bangkok) in 2019, 2020 and 2021 were 1,032.04, 976.76 and 888.40 per 100,000, respectively. The public health region 1, which includes Phrae province had the highest prevalence of 12 public health regions. The prevalence of COPD in those over 40 year in Phrae province in 2019, 2020 and 2021 was 1,341.36, 1,273.71 and 1,038.68 per 100,000, respectively, higher than mean prevalence for the 12 public health regions combined (17).

In 2020, lung cancer was the second most common cancer in the word (11.7%), with new cases estimated at about 2.3 million (11.7%). Lung cancer was the leading cause of cancer death, about 1.8 million cancer-related deaths (18%); deaths from lung cancer is projected to reach 2.45 million worldwide by 2030. Lung cancer was the most frequent cancer in men (14.3%) and the foremost cause of cancer death in men (21.5%) in 2020. It was also the third most common cancer in women (8.4%) and the second most common cause of cancer death in women (13.7%). The five-year survival rate for all types of lung cancer in middle-income countries is about 19%, which is lower than other cancers such as the colon (71%), breast (85%) and prostate (98.9%) cancers (18,19). The incidence of lung cancer worldwide in the general population in 2020 was about 39 per 100,000 in males and 18.2 per 100,000 in females (11). The global incidence rate of lung cancer in both sexes has been reported about 0.06-0.12% per person-year (20,21). In Thailand, lung cancer was the second most common cancer in males and the fourth most common cancer in females in 2016-2018. The mean annual incidence rate of lung cancer in Thailand and in the northern region of the country during 2016-2018 was 22.8 and 33.1 per 100,000 in males, 11.5 and 19.9 per 100,000 in females, respectively (22). The incidence rates of lung cancer in Phrae province in 2019, 2020 and 2021 were 26.7, 20.2 and 21.6 per 100,000/year, respectively in individuals with age over 40 years (about 0.02% per person-year) (17). Previous studies have reported the incidence rate of lung cancer in COPD patients to be about 0.8-1.7% per person-year which is higher than in the general population (23,24). A recent study in Japan reported the incidence of lung cancer in COPD patients who had an annual chest computed tomography (CT) scan was about 1.85% per person-year (25). The incidence of lung cancer in COPD patients in Thailand remains uncertain and there has been no published estimate of the incidence of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital.

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) has issued recommendations for selection of groups for lung cancer screening. The Guidelines recommend lung cancer screening using low-dose computed tomography (LDCT) for individuals with high-risk factors including current and former smokers aged 55 to 74 years with a 30 or more pack-year history of smoking

tobacco, those who quit smoking less than 15 years and individuals aged 50 years or older with a history of smoking 20 or more pack-year who also have at least one additional risk factor (other than second-hand smoke). Additional risk factors include history of lung cancer or lung disease, a family history of lung cancer, exposure to radon, and occupational exposure to carcinogens (26). These guidelines are based on the ability of LDCT to detect early stage lung cancer and to improve mortality outcomes.

Most previous guidelines did not recommend CXR for routine lung cancer screening (27), although some studies have suggested that routine annual CXR screening of high-risk patients can detect a significant number of lung cancer cases. Nevertheless, no studies of mortality outcome improvement from lung cancer screening with CXR have been published (28). LDCT is still recommended for lung cancer screening in high risk population due to the reduction of lung cancer mortality, but LDCT also gives false-positive results leading to unnecessary tests and invasive procedures (29). LDCT has higher sensitivity for detecting lung cancer in early stage, improve mortality outcomes and has been shown to be cost-effective in many countries in Europe, the United States and Canada. However, in other countries, e.g., Australia, which use The National Lung Screening Trial (NLST) criteria, lung cancer screening with LDCT did not demonstrate the cost effectiveness (30). A 2019 study showed the annual lung cancer screening by CXR resulted in higher benefits for the exclusion of lung cancer in repeat patients more than first time patients (31). CXR is simple to use, readily available, and inexpensive, making it suitable for low to middle income countries such as Thailand. This study aimed to estimate the incidence of lung cancer in COPD patients, to identify the associated prognostic factors, to conduct a survival analysis and to determine the benefits of annual CXR screening for lung cancer in COPD patients in Thailand.

METHODS

Population

This study was conducted at the COPD Clinic of the Medicine Unit, Phrae Hospital, in northern Thailand. The retrospective cohort study was conducted between June 1, 2017 and November 30, 2020 for study period with six months continued follow-up period to June 1, 2021. Patients who had registered with the COPD clinic before the start of the study, were age over 40 years, and had no prior CXR evidence of lung cancer were enrolled. Annual CXR during study were required to be officially reported by a radiologist. Patients diagnosed with lung cancer and those having a history of lung cancer were excluded. Patients who did not complete an annual CXR during study and those who had a short duration follow-up period less than six months were also excluded. Data were collected from the hospital database and medical records.

Study protocol

At the enrollment time, the information of COPD patients was recorded including age, sex, weight, BMI, smoking status, family history of lung cancer, comorbidities including diabetes (DM), hypertension (HT), ischemic heart disease (IHD), dyslipidemia (DLP), cerebrovascular accident (CVA), chronic kidney disease (CKD), pulmonary tuberculosis, bronchiectasis, other cancers, duration of COPD diagnosis, FEV1% (Forced expiratory volume in one second) post-bronchodilator, FEV1/FVC (Forced Vital Capacity) post-bronchodilator, CAT (COPD assessment test) score, MMRC (Modified Medical Research Council) dyspnea scale, 6MWT (Six Minute Walk Test), COPD group (A, B, C, and D) and COPD grade (GOLD 1, GOLD 2, GOLD 3 and GOLD 4) which were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (32), laboratory test results including WBC (white blood cell) count, eosinophil count, GFR (glomerular filtration rate), CXR and chest CT scan findings (if available).

During the study period, the following data was recorded included annual CXR findings, exacerbation per person-year, inhaler medication used during the study including LABA (long acting beta2 agonist), LAMA (long acting muscarinic antagonist), LABA/ICS (combination of long acting beta2 agonist plus inhaled corticosteroids), LABA/LAMA (combination of long acting beta2 agonist plus long acting muscarinic antagonist), date and duration of lung cancer diagnosis with histopathological confirmation and lung cancer staging including

NSCLC classification using the TNM classification (33,34) stages IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA and IVB and clinical staging of SCLC into limited and extensive stage (35,36), and treatment and management for COPD patients who developed lung cancer.

End of study data, including number and date of patient deaths, follow-up status at the end of the study and length of follow-up period were also recorded.

This study protocol was approved by the Institutional Ethics Committee of Phrae Hospital.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 23 was used for descriptive data analysis. Categorical data are reported as frequency and percentage, numeric data are reported as mean and standard deviation (SD). Comparison between groups was done using the Student's t-test, the chi-square test, and Fisher's exact test. Univariate and multivariate logistic regression analysis of prognostic factors and lung cancer development are reported as relative risk (RR) and 95% confidence interval (95%CI). The survival curve was calculated using the Kaplan-Meier method.

RESULTS

A total of 345 COPD patients who were existing cases and who were registered in the COPD Clinic before 1 June 2017, with age over 40 years and no prior CXR evidence of lung cancer were initially enrolled. One patient was excluded due to a history of lung cancer. During the study period between 1 June 2017 and 30 November 2020, 19 patients were excluded due to missing complete annual CXR and 9 patients were excluded due to a short follow-up period of less than 6 months. Finally, 316 COPD patients were analyzed and follow-up was continued for 6 months until 1 June 2021 (Figure 1).

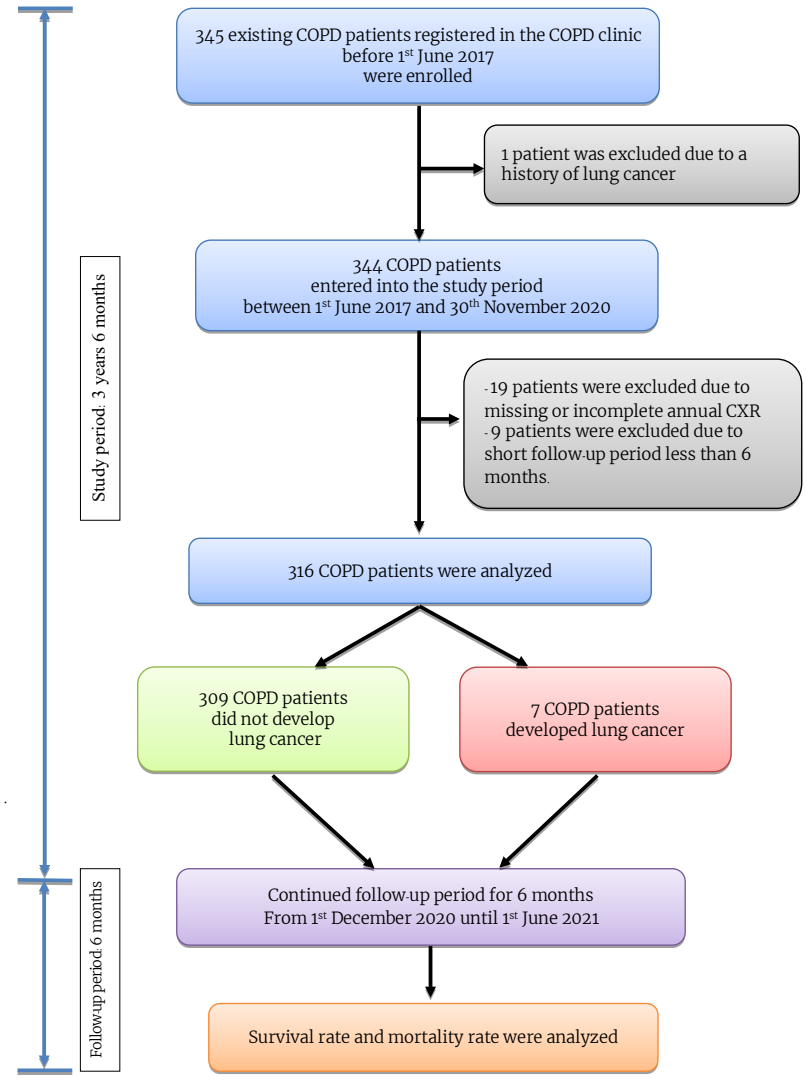

Figure 1. Study flow of COPD patients entered into the study

Table 1. Baseline clinical characteristics of COPD patients in the study and comparison between the lung cancer and without lung cancer groups

Characteristic	Total N=316	Lung cancer group N=7	Without lung cancer group N=309	*p*-value
Age (year, mean±SD)	71.61±10.19	70.86±8.81	71.63±10.25	0.843
Min 44, max 96				
Sex, n (%)				
Male	248 (78.48)	5 (71.42)	243 (78.64)	0.657
Female	68 (21.52)	2 (28.58)	66 (21.36)	
BMI (mean±SD)	20.59±4.64	18.97±4.41	20.63±4.65	0.350
Family history of lung cancer, n (%)	14 (4.43)	1 (14.29)	13 (4.21)	0.274
Smoking status, n (%)				
Nonsmoker	131 (41.46)	0 (0.00)	131 (42.39)	0.044*
Smoker	185 (58.54)	7 (100.00)	178 (57.61)	
- Past smoker	183 (57.91)	7(100.00)	176 (56.96)	1.000
- Current smoker	2 (0.63)	0 (0.00)	2 (0.65)	
Comorbidities, n (%)				
Diabetes mellitus (DM)	30 (9.49)	0 (0.00)	30 (9.71)	1.000
Hypertension (HT)	86(27.22)	3 (42.86)	83 (26.86)	0.395
Ischemic heart disease	19 (6.01)	0 (0.00)	19 (6.15)	1.000
Dyslipidemia	5 (1.58)	0 (0.00)	5 (1.62)	0.995
Cerebrovascular accident	4 (1.27)	0 (0.00)	4 (1.30)	1.000
Chronic kidney disease	4 (1.27)	1 (14.29)	3 (0.97)	0.086
Pulmonary tuberculosis	31 (9.81)	1 (14.29)	30 (9.71)	0.530
Bronchiectasis	4 (1.27)	0 (0.00)	4 (1.30)	1.000
Other cancers	7 (2.22)	0 (0.00)	7 (2.27)	1.000
COPD duration before study (year, mean±SD)	5.61±2.73	3.57±0.79	5.66 ±2.73	0.045*
FEV1 (%), (mean±SD)	62.09±23.38	55.29±17.52	62.25 ± 23.49	0.437
Post-bronchodilator				
FEV1/FVC (mean±SD)	0.58±0.12	0.61±0.11	0.58±0.12	0.542
Post-bronchodilator				
CAT score (mean±SD)	13.52±6.81	14.14±8.39	13.50±6.78	0.806
MMRC (mean±SD)	1.6±0.86	1.86±1.07	1.6±0.86	0.429
6MWT (metre, mean±SD)	275.92±116.20	230.00±165.44	276.48±115.84	0.492
COPD group, n (%)				
A	10 (3.17)	0 (0.00)	10 (3.23)	0.749
B	55 (17.40)	2 (28.57)	53 (17.15)	
C	73 (23.10)	2 (28.57)	71 (22.98)	
D	178 (55.33)	3 (42.86)	175 (56.63)	
GOLD grade, n (%)				
GOLD 1	80 (25.31)	1 (14.28)	79 (25.57)	0.400
GOLD 2	123 (38.92)	2(28.57)	121 (39.16)	
GOLD 3	92 (29.11)	4 (57.14)	88 (28.48)	
GOLD 4	21 (6.65)	0(0.00)	21 (6.80)	
Hemoglobin (g/dL)	12.59±2.29	11.46±2.85	12.61±2.28	0.188
Hematocrit (%), n (%)	38.27±6.58	34.70±7.88	38.35±6.54	0.148
WBC (/µL) (mean±SD)	10,163.77±5338.23	14,000.00±6954.85	10,076.86±5278.26	0.054
Eosinophil (/µL) (mean±SD)	539.11±629.41	243.14± 327.16	545.82±633.27	0.209
GFR (mL/min/1.73 mm^2) (mean±SD)	76.64±22.30	72.06±29.23	74.70±22.18	0.757

BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD assessment test (0-40); MMRC, modified Medical Research Council dyspnea scale (0-4); 6MWT, Six Minute Walk Test; WBC, white blood cell; GFR, glomerular filtration rate

Note: - The classification of COPD Groups A-D by symptoms (MMRC and CAT) and risk of exacerbation history, based on GOLD guideline (32)

- The classification of airflow limitation severity in COPD; GOLD 1=mild (FEV1 ≥ 80% predicted), GOLD 2=moderate (50% ≤ FEV1 < 80% predicted), GOLD 3=severe (30% ≤ FEV1< 50% predicted), GOLD 4 = very severe (FEV1< 30% predicted), based on GOLD guideline (32)

The baseline characteristics of 316 enrollees are showed in Table 1. There were 248 males (78.5%) and 68 females (21.5%). The mean age of the patients was 71.6±10.2 years. The mean duration for COPD was 5.6±2.7 years. Baseline CXR reports showed old pulmonary TB scar, bronchiectasis and emphysema in 31 (9.81%), 4 (1.27%) and 64 (20.25%) of the COPD patients, respectively. Most of the COPD patients were in GOLD group D (55.33%) and GOLD grade 2 (38.92%). Seven COPD patients were newly diagnosed with lung cancer during the 3.5 years study period. The incidence rate of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital was 0.69% per person-year. Most of COPD patients in the lung cancer group were classified in COPD group D (42.9%) and GOLD grade 3 (57.1%).

Baseline clinical characteristic of patients with and without lung cancer were similar in the two groups (Table 1), including age, sex, weight, BMI, family history of lung cancer, comorbidities (DM, HT, IHD, DLP, CVA, CKD, pulmonary tuberculosis, bronchiectasis, other cancers), FEV1(%) post-bronchodilator, FEV1/FVC post-bronchodilator, CAT score, MMRC dyspnea scale, 6MWT, COPD group (A, B, C, and D) and COPD grade (GOLD 1, GOLD 2, GOLD 3 and GOLD 4), laboratory testing results including WBC count, eosinophil count and GFR. This study found that smoking was a significant prognostic factor for lung cancer in COPD patients (p-value 0.044). However, there was no statistically significant correlation in the incidence of developing lung cancer between current smoker and past smoker COPD patients. There were 131 COPD patients (41.46%) who were nonsmokers, 65 of whom (49.62%) were second-hand smokers, 42 (32.06%) were occupationally exposed to particulate matter, 14 (10.69%) were exposed to indoor air pollution from cooking with biomass and 10 (7.63%) had a history of chronic bronchitis and respiratory infection. Duration for COPD diagnosis prior to the study was significantly lower in patients with lung cancer (p = 0.045) but the age of COPD onset was higher in the lung cancer group.

Table 2 shows clinical characteristics of COPD patients during the study, including comparison between the lung cancer and without lung cancer groups. Inhaler medications used during the study, including LABA, LAMA, LABA/ICS and LABA/LAMA were similar in both groups. Exacerbation rate was not statistically significantly different between the groups. Patients in the without cancer group were followed-up significantly longer than the lung cancer group (p = 0.002). The follow-up period in patients without lung cancer was statistically significant longer than those with lung cancer (p = 0.042), because some patients in lung cancer group were loss to follow-up and some patients died

Table 2. Clinical characteristics of COPD patients during the study and comparison between the lung cancer and without lung cancer groups

Characteristic	Total (N=316)	Lung cancer group (N=7)	Without lung cancer group (N=309)	p-value
LABA used during study, n (%)	8 (2.53)	1 (14.28)	7 (2.27)	0.166
LAMA used during study, n (%)	199 (62.97)	5 (71.43)	194 (62.78)	1.000
LABA/ICS used during study, n (%)	276 (87.34)	5 (71.43)	271 (87.70)	0.218
LABA/LAMA used during study, n (%)	34 (10.76)	1 (14.28)	33 (10.68)	0.553
Exacerbation during study (person/year)	0.83	0.46	0.83	0.620
Follow-up status at the end of study, n (%)				
Follow-up	229 (72.46)	1 (14.28)	228 (73.79)	0.002*
Loss follow-up	61 (19.30)	2 (28.57)	59 (19.09)	0.624
Referred	3 (0.95)	0 (0.00)	3 (0.97)	1.000
Death, n (%)	23 (7.28)	4 (57.14)	19 (6.15)	0.001*
Follow-up period (day, mean±SD)	1320.96±279.33	851.57±494.05	1,331.59±264.43	0.042*

LABA, long acting beta2 agonist; LAMA, long acting muscarinic antagonist; LABA/ICS, combination of long acting beta2 agonist plus inhaled corticosteroids; LABA/LAMA, combination of long acting beta2 agonist plus long acting muscarinic antagonist

Table 3. COPD patients who developed lung cancer in the study

Case number	COPD GOLD Group/Grade	COPD duration before study (days)	Days before lung cancer diagnosis	Follow-up period (days)	Diagnosis and treatment	Status at the end of study
1 71-yr Male	B GOLD 2	173	98	1,461	NSCLC stage IA (T1bN0M0) underwent LUL lobectomy: pathology report showed adenocarcinoma	Under follow-up
2 87-yr Female	D GOLD 3	93	293	688	RUL mass suspected lung cancer stage IIIA(T3N1M0), denied for further investigation, palliative care treatment	Died (cancer-related) 20th Apr 2019
3 66-yr Female	D GOLD 3	79	438	560	Lung cancer stage IVA with adrenal gland metastasis, denied for further investigation, palliative care treatment	Died (cancer-related) 13th Dec 2018
4 68-yr Male	C GOLD 3	607	185	299	NSCLC stage IIIB, pathology report showed poorly differentiated squamous cell carcinoma (T4N2M0), treated with chemotherapy	Lost to follow-up Last visit 27th Mar 2018
5 61-yr Male	C GOLD 1	271	1,114	1,272	NSCLC stage IVB, pathology report showed squamous cell carcinoma with bone and right adrenal gland metastasis (T3N3M1c), treated with chemotherapy	Died (cancer-related) 24th Nov 2020
6 73-yr Female	B GOLD 2	369	233	341	SCLC extensive stage,treated with complete course chemotherapy and radiation	Lost to follow-up Last visit 8th May 2018
7 70-yr Male	D GOLD 3	148	805	1,340	Lung cancer stage IVA (T2aN2M1a), denied for further investigation, treated with palliative care treatment	Died (cancer-related) 31th Jan 2021

during study.

Table 3 shows details of the 7 COPD patients in the lung cancer group: 2 (28.6%) were in COPD group B, 2 (28.6%) in COPD group C, and 3 (42.9%) in COPD group D. None of the COPD patients in COPD group A were diagnosed with lung cancer. The mean duration of COPD before the study was 248.57±188.09 days. The mean time to lung cancer diagnosis was 452±372.65 days. Four (57.1%), one (14.3%), one (14.3%), and one (14.3%) patient (s) were diagnosed with lung cancer during the first, second, third year of study, and after third year of the study, respectively. The mean follow-up period was 851 ± 494.05 days. The final pathology report revealed 4 patients (57.1%) had lung cancer: 3 had NSCLC (42.9%) (1 adenocarcinoma and 2 squamous cell carcinoma), and 1 patient had SCLC (14.3%). Patients in the NSCLC group were classified as stage IA, IIIB and stage IVB with one patient in each stage and the one patient in the SCLC group was classified as extensive stage. Three COPD patients in the lung cancer group were clinically diagnosed (no pathology report) as they elected for palliative care and no further investigation. Five patients (71.44%) were symptomatic cases, while 2 patients (28.57%) were asymptomatic at the time of lung cancer diagnosis. Three patients (42.9%) died during study period and one (14.3%) died during the follow-up period.

The univariate and multivariate logistic analysis of COPD patients who developed lung cancer is shown in Table 4. Smoking was a statistically significant prognostic factor for lung cancer development (p = 0.044). However, the correlation between smoking and lung cancer could not be analyzed for RR as all COPD patients in the lung cancer group were smokers.

Finally, the survival rate and mortality rate were analyzed. Twenty-three patients (7.3%) died during the study period and follow-up period, 4 (57.1%) were patients with lung cancer and 19 (6.2%) were patients without lung cancer. Three patients with lung cancer died during the study period and 1 patient died during the follow-up period. Eight patients without lung cancer died during the study period and 11 patients died during the follow-up period. The overall mortality rate for the study period and follow-up period combined was statistically significantly higher in patients in the lung cancer group compared with patients without lung cancer (p = 0.001, Table 2). The mortality rate in COPD patients who developed lung cancer was 24.5 % per person-year which is higher than for those who did not develop lung cancer (1.68% per person-year). The survival curve was determined according to the Kaplan-Meier method, compared COPD patients who developed lung cancer and those who did not develop lung cancer in Figure 2. The survival rate was significantly lower in COPD patients who developed lung cancer compared with those who did not develop lung cancer. The crude analysis hazard ratio (HR) for death in COPD patients with lung cancer compared to those without lung cancer was 25.5 (8.51-76.6;95%CI) and in the adjusted analysis, the HR for death in COPD patients with lung cancer compared to those without lung cancer adjusted for age, sex, and smoking status was 16.3 (5.2-51.1;95%CI).

DISCUSSION

Lung cancer and COPD are relatively common health problems. Both lung cancer and COPD have similar symptoms, i.e., cough, dyspnea, fatigue, and weight loss (1). Since the symptoms overlap with those of other respiratory conditions, misdiagnosis of the condition can occur until the cancer reaches an advanced stage, leading to an increase in high mortality outcomes (37). Some studies have reported on the benefits of annual CXR for lung cancer screening (31,38). This study aimed to estimate the incidence of lung cancer in COPD patients who were followed-up in a COPD Clinic and who received an annual CXR.

The incidence rate of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital, was 0.69% per person-year, which is slightly lower than previous reports (0.8-1.7% per person-year worldwide) (23,24). However, that incidence rate is still higher than the general population. This study found that smoking was a significant prognostic factor for lung cancer in COPD patients (p = 0.044). This finding illustrates that COPD patients who have a history of smoking are more likely to develop lung cancer than nonsmokers.

Table 4. Univariate and multivariate logistic analysis for COPD patients who developed lung cancer

Univariate analysis	Lung cancer group (N=7)	Without lung cancer group (N=309)	RR	95%CI	*p*-value
Age, year n (%)					
< 65	2 (28.57)	97 (31.40)	0.877	0.173-4.441	1.000
≥ 65	5 (71.43)	212 (68.60)			
BMI, n (%)					
< 18.5	3 (42.86)	116 (37.54)	1.242	0.383-5.452	1.000
≥ 18.5	4 (57.14)	193 (62.45)			
Comorbidities, n (%)					
With comorbidities,	5 (71.43)	138 (44.66)	0.331	0.065-1.679	0.251
No comorbidities	2 (28.57)	171 (55.34)			
GOLD grade, n (%)					
GOLD 2 (vs GOLD 1)	2 (28.57)	121 (39.16)	0.769	0.071-8.339	1.000
GOLD 3 (vs GOLD 1)	4 (57.14)	88 (28.48)	0.288	0.033-2.520	0.374
GOLD 4 (vs GOLD 1)	0 (0.00)	21 (6.80)	0.988	0.963-1.012	1.000
GOLD group, n (%)					
Group B (vs Group A)	2 (28.57)	53 (17.15)	1.038	0.986-1.092	1.000
Group C (vs Group A)	2 (28.57)	71 (22.98)	1.028	0.989-1.069	1.000
Group D (vs Group A)	3 (42.86)	175 (56.63)	1.017	0.998-1.037	1.000
MMRC score, n (%)					
< 2	2 (28.57)	186 (60.19)	0.272	0.054-1.382	0.124
≥ 2	5 (71.43)	123 (39.81)			
CAT score, n (%)					
< 10	2 (28.57)	102 (33.01)	0.815	0.161-4.132	1.000
≥ 10	5 (71.43)	207 (66.99)			
Smoking status, n (%)					
Smoker	7 (100.00)	178 (57.61)	-	-	0.044*
Nonsmoker	0 (0.00)	131 (42.39)			
Eosinophil (/μL), n (%)					
< 300	5 (71.43)	141 (45.63)	2.911	0.573-14.781	0.255
≥ 300	2 (28.57)	168 (54.37)			
Multivariate analysis			**RR**	**95%CI**	***p*-value**
Age					
≥ 65 (vs < 65)			1.136	0.229-5.640	0.876
BMI					
< 18.5 (vs ≥ 18.5)			1.291	0.295-5.664	0.734
Sex					
Male vs female			0.577	0.118-2.815	0.497
FEV1 (%) post-bronchodilator					
< 50 (vs ≥ 50)			1.989	0.450-8.800	0.365
CAT score					
≥ 10 (vs < 10)			1.023	0.197-5.319	0.979

Previous reviews have reported that lung cancer is a frequent comorbidity in COPD patients. COPD patients are 6.35 times more likely to develop lung cancer than the general population (4). A previous study reported the risk ratio for lung cancer in COPD patients was higher than for other comorbidities, i.e., hyperension, diabetes, or chronic kidney disease. Nevertheless, the prevalence of lung cancer is quite low compared to that of other comorbidities. The current study found the common comorbidities in COPD patients were hypertension (27.2%), pulmonary TB (9.8%), diabetes (9.5%) and ischemic heart disease (6.0%). Prior research has revealed that the age and sex adjustment odds ratio for lung cancer development in COPD patients is quite high (OR = 8.538,7.597-9.595; 95% CI) compared to hypertension (1.60,1.57-1.62; 95% CI) or diabetes (1.55,1.52-1.57; 95% CI) (39). That in this study no statistically sig-

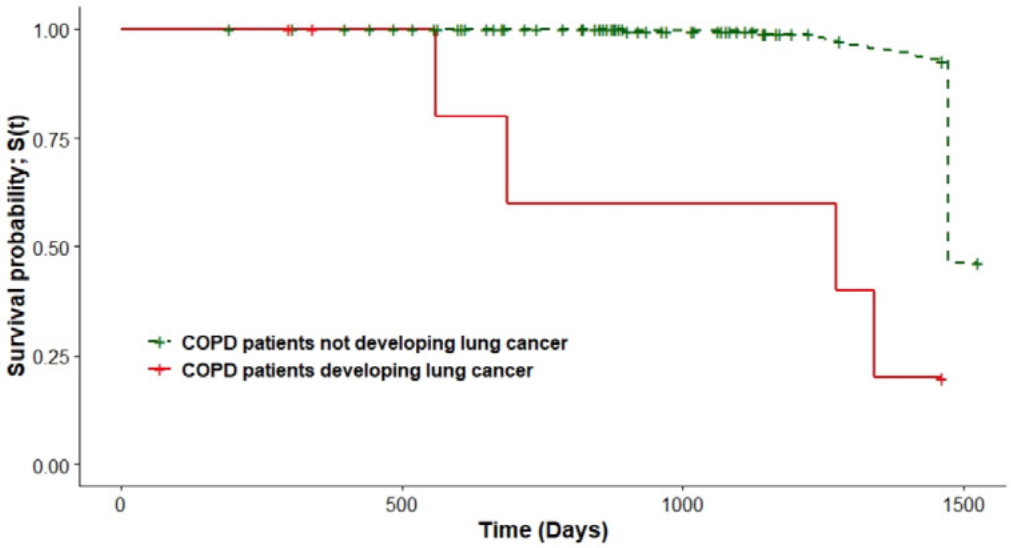

Figure 2. Survival curve using the Kaplan-Meier method to compare between COPD patients who developed lung cancer and those who did not develop lung cancer

nificant relationship between comorbidities and the development of lung cancer was found may be due to the small number of patients in the lung cancer group.

From the demographic data of COPD patients in this study according to the GOLD classification, most of the COPD patients were in GOLD groups C and D which have a greater severity than groups A and B, and most of them were classified in GOLD 2 and GOLD 3. Most of the COPD patients who had lung cancer were in COPD group D (42.9%) and GOLD grade 3 (57.14%). Although, the severity of COPD in terms of GOLD group and grade in this study was not associated with lung cancer, the severity of airflow limitation (GOLD grade 3 and 4) was higher in the lung cancer group but the different was not statistically significant.

For most COPD patients in the lung cancer group, their lung cancer was detected in the first year of study (57.1%). However, only one patient (14.3%) had stage I lung cancer while six (85.7%) had advanced stage lung cancer. These findings indicate that the lung cancer of some of the COPD patients was detected only at an advanced stage despite having undergone routine annual CXR follow-up. This could be because they were asymptomatic in the early phase and the natural course of some types of histopathological lung cancer is later becomes aggressive and spreads quickly, leading to delayed diagnosis of first stage lung cancer. The results showed about 42.9% of COPD patients had NSCLC and 14.3% had SCLC, which is similar to previous studies. In the NSCLC group, the most histopathology cell type was squamous cell carcinoma (66.7%) which is similar to a previous study that reported squamous cell carcinoma was a major cell type in COPD related lung cancer (9).

This study demonstrated that most COPD patients who entered the study had good compliance as 72.5% of them remained in follow-up throughout study. Patients in the without lung cancer group remained in follow-up significantly longer than those in the lung cancer group. About 28.6% of patients in the lung cancer group were lost to follow-up during the study period. Exploration of the details of patients with lung cancer who were lost to follow-up revealed that all of them had an advanced stage of lung cancer; one had stage IIIB NSCLC and was lost to follow-up during chemotherapy and another had extensive stage SCLC and was lost to follow-up after a complete course chemotherapy and radiation.

The survival curve revealed a significant decrease in survival rate among COPD patients with lung cancer (Table 2 and Figure 2). The mortality rate in COPD patients who developed lung cancer was more than ten time higher than those who did not develop lung cancer (24.5% per person-year vs 1.68% per person-year, respectively).

A limitation of this study was that it was not possible to investigate potential prognostic factors for developing lung cancer other than smoking. That may, in part be due to the large difference in number of patients with lung cancer and those without lung cancer, a reflection of the low incidence rate of lung cancer development in the COPD population. If a longer study period and follow-up period are included in future research, additional potential prognostic factors could be investigated. Another limitation was that the study protocol used CXR instead of LDCT for lung cancer screening, leading to a lower incidence of lung cancer compared with previous studies that used LDCT, detecting early stage lung cancer only 1 patient (14.28%). Because CXR is less sensitive than LDCT in detecting lung cancer in early stage, this study found the incidence of lung cancer to be slightly lower than in previous reports. However, CXR is simple to use, readily available, and in expensive, which is suitable for the economic status of Thailand. Finally, there were 3 patients (0.42%) in lung cancer group who had no histopathological confirmation although the clinical symptoms and radiological reports, including CXR and CT scan of chest and abdomen, showed the most likely diagnosis was primary lung cancer rather than other extrapulmonary malignancy with distant pulmonary metastasis.

In clinical practice, routine yearly CXR should be recommended for all COPD patients because of the benefits, easy availability, and low cost in clinical practice (38,40). Although LDCT has greater sensitivity for detecting lung cancer in the early stage, improved mortality outcomes in many countries indicate the cost-effectiveness that method (30). However, LDCT is not practical for use in Thailand except for COPD patients who have been evaluated as being in the high risk group for lung cancer. With those patients, it can be helpful for differentiating cancer from other respiratory disease that can be found in COPD patients, e.g., pulmonary tuberculosis, pulmonary fibrosis, pulmonary fungal infection, and bronchiectasis (32,41).

CONCLUSION

The incidence rate of lung cancer in COPD patients is higher than in the general population and the mortality rate in COPD patients with lung cancer is higher than in patients without lung cancer. An annual CXR should be performed as part of routine lung cancer screening for COPD patients to detect lung cancer. Because CXR has lower sensitivity than LDCT in detecting lung cancer in the early stage, the incidence of lung cancer is slightly lower than previous reports using LDCT. In clinical practice, CXR is simple to use, readily available and inexpensive.

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CONFLICTS OF INTEREST

The author declares no potential conflicts of interest.

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