CLINICAL AND GENETIC ASSOCIATIONS BETWEEN LUNG CANCER AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Thesis submitted in accordance with the requirements of the

University of Sheffield for the degree of Doctor in Philosophy

By

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July 2017

ABSTRACT

Lung cancer and chronic obstructive pulmonary disease (COPD) are both leading causes of death in the world, and these two disease are closely linked in the clinical setting and at the genetic level. Previous studies have indicated that COPD confers a higher risk for development of lung cancer, and also affects prognosis once lung cancer has occurred. The present thesis further explored the influences of timing of COPD diagnosis, severity of airflow limitation, radiological emphysema, and genetic variants on lung cancer outcomes. Over 1,000 patients who were diagnosed with non-small cell lung cancer at Mayo Clinic were included. Near two-thirds of patients with COPD were underdiagnosed at the time of lung cancer diagnosis. In comparison to the previously recognized COPD, an incidentally diagnosed COPD was a major factor that increased risks of postoperative complications (incidental COPD versus non-COPD: 28.1% versus 16.5%, $p<0.01$) and impaired lung cancer survival (HR, 1.23; 95%CI, 1.05-1.45). Patients with moderate (HR, 1.22; 95%CI, 1.04-1.44) to severe airflow obstruction (HR, 1.75; 1.38-2.23) had a significantly poorer long-term outcome, while similar survival was found between patients with mild COPD and with normal lung function ($p=0.97$). The severity of regional emphysema was associated with overall survival in early stage lung cancer ($p<0.01$), which was independent of tumor location, and it was predictive of quality of life related to dyspnea after lung cancer treatment ($p<0.05$). Radiological emphysema was also correlated with postoperative lung function recovery (FEV_1% and DLCO%, both $p<0.05$) when tumor resection was performed in the emphysematous region. Meta-analysis indicated that the negative impact of COPD was more pronounced in patients with non-small cell lung cancer (pooled HR, 1.23; 95%CI, 1.16-1.30), at an early-stage (pooled HR, 1.35; 95%CI, 1.12-1.63), and who received surgical treatment (pooled HR, 1.31; 95%CI, 1.13-1.51). The effects of single nucleotide polymorphisms on lung cancer survival differed by COPD status; SNP rs74798757 was significantly associated with survival from lung cancer with COPD, whereas SNP

rs10218481, *CASP7* rs17090907, *GPC5* rs1409600 and rs163933, and *TAAR8* rs8192627 were independent factors for survival in lung cancer patients who were COPD-free. These results indicate that COPD status may play a significant role in the association between genetic variants and lung cancer outcomes. Further validation from independent cohorts and functional characterization for these associations are necessary, which in future may benefit the COPD-lung cancer population.

ACKNOWLEDGEMENTS

Prof. Gening Jiang, my supervisor has my deepest and sincerest gratitude for his constant support, advice and help. He gave me the invaluable opportunity to finish my Ph.D. study in USA (Mayo Clinic) and UK (the University of Sheffield) where I had privilege of learning from my co-supervisors (Prof. Ping Yang and Prof. Angela Cox) and working together with many colleagues. I would express my sincere thanks for all the continuous care, encouragement, and great freedom that he offered me.

Specific thanks also goes to Ms. Yongmei Yu and my fellow colleagues for sharing their working experience and scientific knowledge with me, and all the support they gave to me.

To Dr. Wenxin He, Dr. Ming Liu, Dr. Nan Song, Dr. Yang Yang, Dr. Xiaoxiong Xu, Dr. Jie Yang, Dr. Siming Jiang, Dr. Yuling Yang, Dr. Yong Yang, Dr. Zhiyi Liu, Dr. Chao Jiang, Dr. Linsong Chen, Dr. Weiwei Xu, Dr. Hongdou Ding, Dr. Xinnan Xu, Dr. Qiuyuan Li, Dr. Kaiqi Jin, Dr. Yingran Shen, Dr. Jinghan Shi, Dr. Jian Can, Dr. Xinsheng Zhu, Dr, Dongliang Bian, Dr. Kaixuan Zhang, Dr. Feng Zhou, Dr. Yunfei Zhang, and Dr. Yanhua Guo.

I am grateful to my co-supervisor Prof. Ping Yang during my study at Mayo Clinic. Most of the present work was carried out under the supervision of Prof. Ping Yang. I deeply express my sincere thanks to Prof. Ping Yang for her suggestions during my Ph.D. study, valuable criticism to manuscripts, and kind treat during our group discussion at weekends.

Sincere thanks also goes to my friend-colleagues for their practical knowledge and technical assistance throughout my study at Mayo Clinic.

To Ms. Shawn Stoddard, Ms. Amy Bennett, Ms. Ruchi Gupta, Mr. Jason Wampfler, Ms. Pamela Neville, Ms. Connie Edwards, Ms. Carol J Greenlee, Ms. Glenda Mueller, Dr. Mingrui Zhang, Dr. Kunlatida Maneenil, Dr. Qiang Lu, Dr. Qian Guo, Dr. Liming Zhao, Dr.

Yi Liu, Dr. Jie Na, and Mr. Tim Skogen.

I would like to extend my sincere thanks to my co-supervisor Prof. Angela Cox for her scientific vision and patient guidance during my writing process of literature review, and for her continued support and enthusiasm during my research in Sheffield. I appreciate her time and effort to help me solve all the problems before I came to Sheffield.

Sincere thanks also goes to my friend-colleagues for their technical assistance and encouragement through the time I have spent in Sheffield.

To. Dr. Shobha Silva, Dr. Rebecca Bastock, Dr. Fiona Taylor, Dr. Clair Fellows, Ms. Helen Cramp, Mr. Daniel Connley, Mr. Ian Brock, Ms. Ms. Amy Shaw, and Dr. Martina Dal.

Moreover, I owe a significant debt of gratitude for the following people for their help, advice and encouragement.

To Dr. Peng Zhang, Dr. Jingyun Shi, Dr. Yiming Zhou, Dr. Haifeng Wang, Dr. Dong Xie, Dr. Alan Sihoe, Dr. Minwei Bao, Dr. Wei Huang, Dr. Xiaogang Liu, Dr. Xuefei Hu, Dr. Yanfeng Zhao, Dr. Xiao Song, Dr. Junjie Zhu, Ms. Jin Zhou, Ms. Hui Li, and Ms. Jia Zhai.

Additionally, my sincere gratitude goes to the staff at the following departments, and many others who cannot be individually acknowledged in such a short space.

Department of Thoracic Surgery, Shanghai Pulmonary Hospital Tongji University
Department of Health Science Research, Mayo Clinic, Rochester, MN
Department of Oncology and Metabolism, Medical School, the University of Sheffield

This study could never have been achieved without all these people.

Finally, I dedicate this thesis to my family, in particular to my mother, my twin brother, and my deceased father and grandma, for their unconditional love and unwavering support.

Publications

From this project

Dai J, Yang P, Cox A, Jiang G. Lung cancer and chronic obstructive pulmonary disease: From a clinical perspective. Oncotarget 2017;8(11):18513-18524.

Dai J, Liu M, Swensen SJ, Stoddard SM, Wampfler JA, Limper AH, Jiang G, Yang P. Regional Emphysema Score Predicting Overall Survival, Quality of Life and Pulmonary Function Recovery in Early-stage Lung Cancer Patients. J Thorac Oncol 2017;12:824-832.

Dai J, Liu M, Jiang G, Yang P. The Impact of Chronic Obstructive Pulmonary Disease on Lung Cancer Survival: A Meta-analysis. Arch Cancer Res 2016;4:1.

Others

Dai J, Zhu X, Bian D, Fei K, Jiang G, Zhang P. Surgery for predominant lesion in nonlocalized bronchiectasis. J Thorac Cardiovasc Surg 2017;153:979-985.

Dai J, Jiang G. Lymphadenectomy in Pulmonary Metastasectomy: For Diagnostic Purpose or Therapeutic Effect? Ann Thorac Surg 2017;103:688.

Dai J, Xie D, Wang H, He W, Zhou Y, Hernandez-Arenas LA, Jiang G. Predictors of survival in lung torsion: A systematic review and pooled analysis. J Thorac Cardiovasc Surg 2016;152:737-745.

Dai J, Shi J, Soodeen-Lalloo AK, Zhang P, Yang Y, Wu C, Jiang S, Jia X, Fei K, Jiang G. Air bronchogram: A potential indicator of epidermal growth factor receptor mutation in pulmonary subsolid nodules. Lung Cancer 2016;98:22-28.

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List of Abbreviations

6MWD	6-min walk distance
AATD	α-1 antitrypsin deficiency
BMI	body mass index
CCI	Charlson comorbidity index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
DLCO	diffusion capacity of lung for carbon monoxide
EGFR	epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
FEV_1	forced expiratory volume in one second
FDR	false discovery rate
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GWA	genome-wide association
HDI	human development index
HR	hazard ratio
HWE	Hardy-Weinberg equilibrium
IASLC	International Association for the Study of Lung Cancer
ICS	inhaled corticosteroids
ILCCO	International Lung Cancer Consortium
ILD	interstitial lung disease
LDCT	low-dose computed tomography
LVRS	lung volume reduction surgery
MAF	minor allele frequency
MDT	multidisciplinary treatment

MMP	matrix metalloproteinase
nAChR	neuronal nicotinic acetylcholine receptors
NLST	National Lung Screening Trial
NSCLC	non-small cell lung cancer
OR	odds ratio
OS	overall survival
PFT	pulmonary function test
PPC	postoperative pulmonary complication
QOL	quality of life
RES	regional emphysema score
RR	relative risk
RV	residual volume
SBRT	stereotactic body radiotherapy
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
SHS	secondhand tobacco smoke
SNP	single nucleotide polymorphism
TLC	total lung capacity
USPSTF	United States Preventive Services Task Force
VO_{2peak}	peak oxygen uptake

CHAPTER ONE

INTRODUCTION

1.1 Lung Cancer

Lung cancer is one of the most devastating diseases and it imposes a major disease burden on the world. According to cancer statistics research in United States, lung cancer ranks second among all newly diagnosed cancer, after prostate cancer (21% of all cancers) in males and breast cancer (29% of all cancers) in female, respectively[1]. However, lung cancer is the greatest cause of cancer-related death, which accounts for one-quarter of all cancer deaths globally; it kills almost twice as many women as breast cancer and more than three times as many men as prostate cancer[1]. A report from World Health Organization has shown that lung cancer remains the most common cancer and the leading cause of cancer death in China and across the world (Figure 1.1).

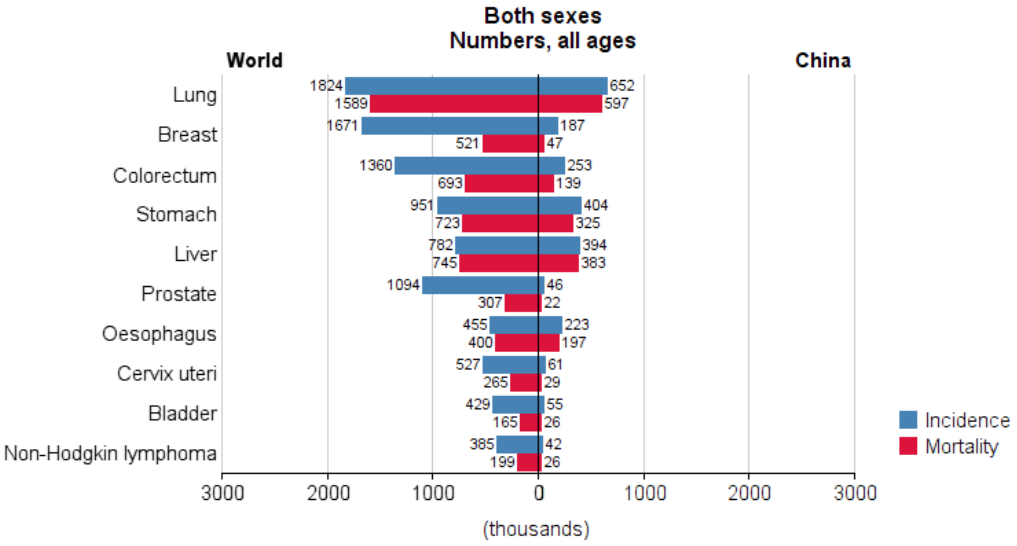


Figure 1.1: Ten leading cancer types for cancer incidence and mortality. 2012 International Agency for Research on Cancer. Available from URL: http://globocan.iarc.fr/Pages/online.aspx (Accessed March 9, 2017).

In addition, lung cancer is the most 'expensive' cancer; it constitutes 15% of overall cancer costs worldwide[2]. The lost productivity due to lung cancer mortality (27% of total cost) is more than the next four costliest cancers (colorectal cancer, 9%; breast cancer, 8%; pancreas cancer, 5%; and leukemia, 4%) combined[3].

Lung cancer incidence has steadily increased from 2002 to 2012[4,5], and is predicted to continue to increase in the near future[1,6]. Nevertheless, with an increasing awareness of the health hazards of smoking and enforcement of tobacco control policies, alongside the implementation of low-dose computed tomography (LDCT) in lung cancer screening, there have been substantial changes in the pattern of incidence of lung cancer across the world over the past decades.

1.1.1 Epidemiology

1.1.1.1 Gender

Lung cancer has traditionally stood out as a predominantly male disease[7]; however, it has been increasingly recognized that women appear to have a greater susceptibility to tobacco carcinogens, but have a lower rate of fatal outcomes of lung cancer compared to men[8]. Biological explanations for gender differences in lung cancer include reproductive and hormonal factors and difference in the sex chromosomes between female and male[9,10]. Several epidemiologic studies have indicated that there has been a significant downward trend among men and a dramatic increase in the incidence of lung cancer in women during the past 50 years[4,11,12], contributing to incidence rates for males and females gradually converging over time[5]. This is primarily because of the high prevalence of exposure to secondhand smoke and biomass fuels among women[13,14]. It is also anticipated that gender equality in lung cancer incidence rates will be attained in the coming future[15]. The recognition of the temporal changes in gender distribution may have potentially valuable implications in clinical trial design as many genetic mutations targeted for new drug development are highly related to gender, such as epidermal growth factor receptor[16].

1.1.1.2 Histologic type

Lung cancer is typically divided into two major histologic types: small cell lung cancer and non-small cell lung cancer (NSCLC), and adenocarcinoma, squamous cell carcinoma, and large cell carcinoma constitute the three main NSCLC subtypes[17]. In parallel with the gender-specific changes in incidence pattern, histologic type distribution has also shifted over time. Until early 1980, squamous cell carcinoma was most prevalent in men, and the most common type of lung cancer reported in United States, Europe, and Asian countries[18-20]. Now, in almost every epidemiologic study, adenocarcinoma has overtaken squamous cell carcinoma as the most common form of lung cancer in both men and smoking population[5,21], and has remained the dominant pathologic type diagnosed among females[22]. Modifications to cigarette composition and smoking behavior are believed to account for the histological shift towards adenocarcinoma[18], because smoke from lower yield cigarettes (i.e., low tar, low nicotine, or filtered) tends to be inhaled more deeply, resulting in a higher concentration of carcinogens in the peripheral lungs where adenocarcinomas s usually occur[23].

The US age-adjusted incidence rate of small cell carcinoma rose though the mid-1980s and peaked in the early 1990s, reaching 11 cases per 100,000 person-years[12]. Meanwhile, the proportion of women increased, from 28% of all small cell carcinomas in 1973 to 50% in 2002[24]. Since then, there has been a roughly parallel decrease in the incidence rates of small cell lung cancer among both males (9.8 per 100,000 person-years) and females (7.9 per 100,000 person-years)[25]. By contrast, the proportion of small cell lung cancer (among all lung cancer histologic types) has steadily increased in Chinese males (from 13.8% to 15.0%) but stabilized among Chinese women (approximately 10.2%) from 2000 to 2012[26,27].

Large cell carcinoma is an ambiguous tumor entity that lacks any specific features

of small cell carcinoma, adenocarcinoma, and squamous cell carcinoma[28]. It is the least frequent subtype of lung cancer (less than 10%), and is considered to be a diagnosis of exclusion[29]. Data from the Surveillance, Epidemiology, and End Results (SEER) database indicates that the incidence rate of large cell carcinoma has declined drastically since the late 1980s, with only 1 case per 100,000 person-years in 2010[12]. However, this trend data is most likely due to the change in diagnostic criteria and improvement in immunohistochemistry and molecular analysis.

1.1.1.3 Geographic region

Lung cancer incidence varies across continents, and is generally more common in the developed world (Figure 1.2)[30]. In males, the highest lung cancer incidence rates are reported in the United States and Eastern Europe, while in women, the highest rates are found in North America and parts of Europe (including United Kingdom)[31]. By socioeconomic grouping (based on the Human Development Index (HDI), a composite measure of population health, knowledge, and living standards) the incidence rate is highest in the countries with a very high HDI (e.g., United States, United Kingdom, Sweden, and Spain), followed by countries with a medium HDI (e.g., India and South Africa), then those with a high HDI (e.g., Russia and Iran), and is lowest in those with a low HDI (e.g., Cameroon and Kenya)[5].

Although the incidence rate of lung cancer currently remains high worldwide, the global burden of lung cancer has shifted towards less developed countries[4,32]. A dramatic rise in the incidence of lung cancer in China is particularly noticeable[6]. In fact, international variations and trends in lung cancer rates largely reflect the changes in the tobacco epidemic because smoking accounts for more than 80% of lung cancers in men and 50% of lung cancers in women[33]. In contrast to several western countries where comprehensive national tobacco control measures have been developed and

implemented[34], the consumption of cigarettes is still growing steadily in China[35], resulting in an upward trend in lung cancer incidence. Estimates indicate that by 2030, 70% of tobacco-related deaths will occur in developing countries[36].

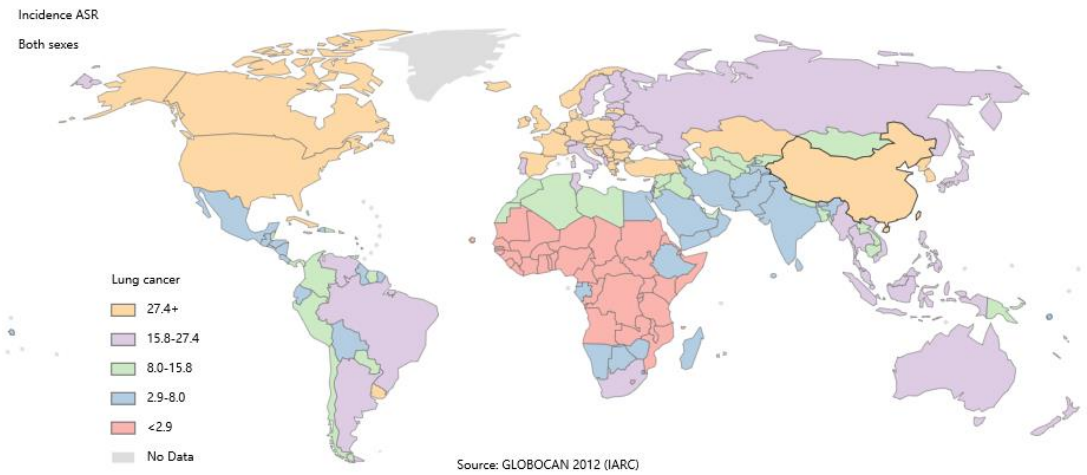


Figure 1.2: The worldwide incidence of lung cancer in 2012 among both sexes. International Agency for Research on Cancer. Available from URL: http://globocan.iarc.fr/Pages/online.aspx (Accessed March 10, 2017).

1.1.2 Risk factors

The development of lung cancer can be conceptualized as the joint consequence of the interaction between exposure to etiologic agents and individual intrinsic susceptibility[37]. Lung cancer has an important heritable component[38]. Although individual genetic variations are not modifiable, they can serve as potential targets to define the high-risk population and improve primary prevention for lung cancer[39] (which will be discussed in the next chapter). However, there are still large knowledge gaps in the perception of lung cancer amongst the general population[40]; the majority consider lung cancer to be tobacco-induced while a minor proportion regard it as an environment-associated disease[40]. The following section focuses mainly on tobacco smoking and environmental risk factors (occupational exposure and air pollution), and

previous lung disease is also considered, given that its role in lung cancer development has been increasingly recognized.

1.1.2.1 Tobacco smoking exposure

Tobacco smoking is by far the most important and evident etiologic factor for all major histological types of lung cancer[41,42]. The carcinogenic effect of tobacco on the lung was described for the first time in early 1950s[43]. It has been estimated that around 80% and 50% of lung cancer cases in men and women are caused by smoking, respectively[44]. A recent meta-analysis quantified the relationship of smoking with lung cancer risk, clearly demonstrating an elevated risk of lung cancer among current smokers (relative risk [RR], 8.43; 95%CI, 7.63-9.31) and ex-smokers (RR, 4.30; 95%CI, 3.93-4.71)[45]. Moreover, a dose-response relationship has been observed where the risk of cancer developing increases as the amount and duration of smoking increase, and with earlier starting age[41,45]. As discussed above, the low-yield cigarettes have caused a shift in the site of disease as well as in the histology of lung cancer, but there is a lack of information about their impact on overall lung cancer risk compared to higher tar cigarettes. The favorable effect of tobacco cessation is enormous[34,46]; however, the residual risk for lung cancer may persist even in those who have quitted for as long as 15 years, as indicated by both hospital- and community-based studies[47,48].

In addition to voluntary tobacco smoking, exposure to secondhand smoke (i.e., passive smoking) is another smoking-related cause of lung cancer, which increases risk of lung cancer by 31% (95%CI, 17-45%) when compared to those never exposed[49]. Moreover, this association holds true among both ever smokers and never smokers, and regardless of cancer histological type and source of exposure (residential or workplace)[41,50,51]. A linear relationship is also noted between lung cancer risk and both the duration of exposure and the quantity of cigarettes smoked by smoking partner[52].

It has been reported that approximately 40% of children, 35% of women, and 33% of men are regularly exposed to secondhand smoke[53]. In fact, secondhand smoke has become an important issue across all countries and caused almost 603,000 deaths worldwide in 2004 (including 21,400 lung cancers attributable to secondhand tobacco exposure)[53].

1.1.2.2 Occupational exposures

Occupational exposures play an important role in lung cancer etiology, and the respiratory system is the most vulnerable site of occupationally-acquired malignancy[41]. It has been estimated that around 10% of lung cancers result from occupational agents[54]. The International Agency for Research on Cancer (IARC) has documented 12 common occupational lung carcinogens, of which evidence for asbestos, silica, radon, heavy metals and polycyclic aromatic hydrocarbons is the most well-established.

The risk of lung cancer is observed to increase with increased exposure to asbestos, with an RR for lung cancer of 3.49 (95%CI, 1.69-7.17) after controlling for age and smoking status[33]. Moreover, a 37-year cohort study on 577 workers exposed to asbestos in China showed a significantly greater risk of lung cancer death in the asbestos workers when compared with the control workers (age and smoking-adjusted HR, 3.31; 95%CI, 1.60-6.87)[55]. Concurrent cigarette smoking and asbestos can act synergistically to greatly increase lung cancer risk[41]. Silica is considered to be one of the most serious occupational hazards to workers' health, and leads to silicosis. It has been reported that more than 33 million workers are exposed to crystalline silica dust in China. The association of silica exposure with lung cancer risk was recently confirmed by a meta-analysis, where the carcinogenic role of silica was more pronounced at higher levels of exposure and in the presence of silicosis (pooled standardized incidence ratio, 2.49; 95%CI, 1.87-3.33)[56]. Radon has come to attention

in recent years because it is recognized as a ubiquitous indoor air pollutant[37]. For occupational radon exposure, such as underground miners of uranium, an increased risk of lung cancer has been well documented[57]. Like asbestos, smoking synergistically modifies the carcinogenic effect of radon[58].

Exposures to heavy metals are commonly seen in nickel miners, workers in cadmium-based battery manufacture, and chromate production workers, and studies on these heavy metals (cadmium, nickel, and chromium) have shown an increased risk of lung cancer[59]. A recent health assessment report from China revealed that, in heavily industrialized urban environments, chromium, cadmium and cobalt also posed lifetime lung cancer risks to local residents[60]. Polycyclic aromatic hydrocarbons (PAH) are a complex group of chemicals that derive from the incomplete combustion of organic materials. An excess risk of respiratory tract cancer (mainly lung cancer) has been reported in PAH-related occupations by a recent meta-analysis and systematic review[61,62], including iron and steel foundries (pooled RR, 1.31; 95%CI, 1.08-1.59), coal gasification (pooled RR, 2.39; 95% CI 1.36-4.21), and aluminum production (pooled RR, 1.29; 95% CI 1.12-1.49).

1.1.2.3 Air pollution

Outdoor air pollution is a complex mixture containing a number of hazardous compounds, many of which come from vehicle exhaust and industrial burning of waste[44], and has been associated with increases in both lung cancer incidence and mortality[63,64]. It is estimated that 8% of global lung cancer deaths can be attributed to exposure to fine particulate matter (PM) alone[65]. $PM_{2.5}$, defined as particles 2.5µm or less in diameter, has caught much attention due to its ability to penetrate deep into the respiratory tract (Figure 1.3)[63]. A recent systematic review by the International Agency for Research on Cancer (IARC) that combined 14 studies indicated a positive

association for $PM_{2.5}$ with lung cancer risk (meta-RR, 1.09; 95%CI, 1.04-1.14), with a greater meta-estimate of 1.40 (95%CI, 1.07-1.83) if only adenocarcinoma of the lung is considered[66]. The RR of lung cancer promoted by air pollution seems generally small, but the attributable risk (RR multiplied by the number of exposed people) is significant[63]. Therefore, effective policies to control the sources of air pollution should be implemented, to reconcile the need for industrial development with concern for public health.

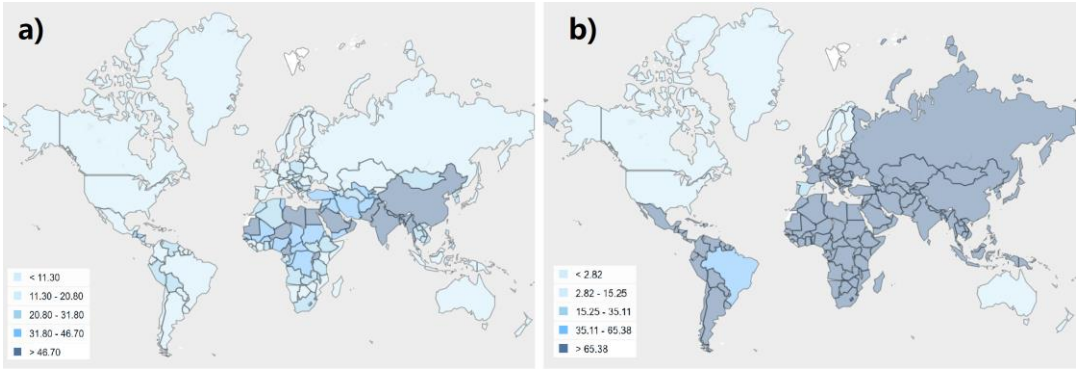


Figure 1.3: Global level of $PM_{2.5}$ air pollution. (a) mean annual exposure (micrograms per cubic meter); (b) population exposed to levels exceeding WHO guideline value (% of total). Available from URL: http://www.worldbank.org/ (Accessed March 21, 2017).

Indoor air pollution is a major risk factor for lung cancer in never smokers, particularly in women and children as they spend most of their time indoors[67]. Indoor pollutants may originate from biomass fuels burning in poorly ventilated homes in rural households, and also may result from building materials and wall coverings in urban cities[59,67]. Globally, around 2.4 billion people rely on biomass fuels for heating and/or cooking, and a recent meta-analysis of 13 case-control studies further supported a causal relationship between biomass burning and lung cancer risk (overall OR, 1.17; 95%CI, 1.01-1.37)[68]. Indoor exposure to radon is significantly associated with lung cancer[41]. In fact, the current concern about lung cancer risk from radon mainly comes from residential and/or indoor rather than occupational exposure, and lung cancer risk increases in areas of higher level of radon concentration[58]. Apart from the recognized indoor pollutants in developed countries, exposure to fumes from high-

temperature cooking is considered to be an important cause of lung cancer in Chinese women, which is independent of passive smoking[44,69].

1.1.2.4 Pre-existing lung disease

Many respiratory diseases have been demonstrated to confer an increased risk for lung cancer (Figure 1.4)[70-72]. A recent multicenter observational study revealed that about 28.2% of patients with newly diagnosed lung cancer had latent tuberculosis infection[73]. Another nationwide cohort study demonstrated that patients with pulmonary tuberculosis had a standardized incidence ratio (compared to the expected cancer incidence) of 3.55 (95%CI, 3.24-3.89) for lung cancer[74], and the excess lung cancer risk appeared to be concentrated mainly within the first 3 years after the diagnosis of tuberculosis[75]. Evidence for the relationship between pulmonary tuberculosis and lung cancer was further strengthened by the two recent meta-analyses[71,72]. An increased lung cancer risk was also implicated in patients with bronchiectasis[76], but the connection is not well studied. Contrary results indicated that pre-existing bronchiectasis was associated with a lower risk of lung cancer in the same lobe and when accompanying chronic obstructive pulmonary disease[77,78]. Interstitial lung disease (ILD), represented by idiopathic pulmonary fibrosis (IPF) and connective tissue disease-related ILD, is associated with lung cancer. Several studies have reported a high prevalence of lung cancer in patients with ILD, ranging from 5.5% to 20.4%[79,80]. Ozawa and colleagues studied 103 IPF patients without lung cancer at the time of their initial diagnosis, and found the cumulative incidence of lung cancer was 15.4% at 5 years, and the median duration was 120.0 months from IPF diagnosis to the development of lung cancer[79]. A high lung cancer incidence was detected in heavy smokers hospitalized to due to community-acquired pneumonia, with 1-year cumulative incidence of lung cancer being 8.14%[81]. Additionally, in contrast to

bronchiectasis, lung cancer tended to be located in the same lobe as the prior pneumonia[81]. This finding was supported by a pooled analysis from the International Lung Cancer Consortium, which showed a history of pneumonia conferred a 1.57-fold increased risk of lung cancer (95%CI, 1.22-2.01)[72]. The relationship between asthma and lung cancer is still controversial; some studies suggested an increased risk of lung cancer in patients with asthma[82] but others indicated an inverse association[64,83]. A recent study investigated the joint effect of co-existing pulmonary diseases on lung cancer risk, and demonstrated that co-occurrence of chronic bronchitis and emphysema had a stronger positive association with lung cancer than chronic bronchitis alone[64]. The association between chronic obstructive pulmonary disease (COPD) and lung cancer risk will be discussed in detail in the next chapter.

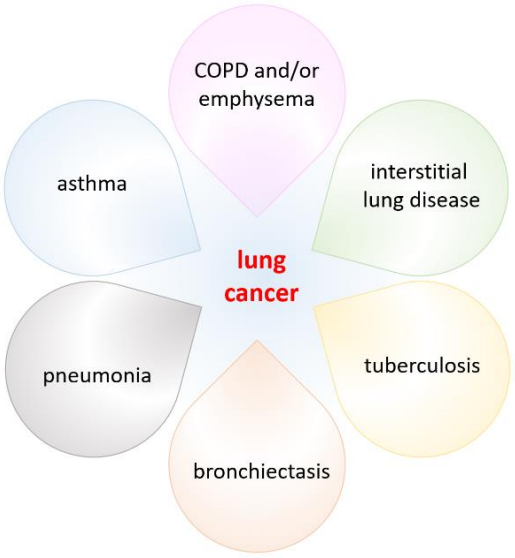


Figure 1.4: Relationship between pre-existing respiratory diseases and lung cancer. COPD: chronic obstructive pulmonary disease.

1.1.3 Prognosis

1.1.3.1 Tumor-related factors

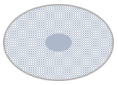
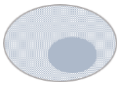
(i) Tumor size

Tumor size plays a significant part in lung cancer prognosis. Recently, TNM staging system was updated to 8th edition based on prognostic data from a multinational study cohort of the International Association for the Study of Lung Cancer (IASLC)[84]. The major changes in this updating are in T category, where T1 classification was subclassified into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm); T2 was subclassified into T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm), emphasizing the prominent role of size in defining the T category[85]. In clinical practice, tumor size can be determined by maximum diameter either on the resected specimen (pathological T stage), or based on the computed tomography scan (clinical T stage), both of which have important prognostic implications. The respective 5-year survivals in node-negative patients were 92%, 86%, 81%, 74%, 65% for pathologically staged T1a-T2b, and 92%, 83%, 76%, 67%, 60% for clinically staged T1a-T2b[85]. In addition, the prognostic significance of tumor size remains in node-positive and/or locally invasive disease[86].

With respect to clinical tumor size, it remains a topic of open discussion as to whether whole tumor size or solid component size provides more prognostic information. Historically, whole tumor size has been regarded as the benchmark for tumor aggressiveness and prognosis[87]. However, recent studies have shown that size of consolidation on CT has a better discriminative ability than whole tumor size in terms of both overall and disease-free survival in early-stage lung cancer[88,89]. Sakakura and colleagues examined the correlation of pathological invasive size with different radiological parameters, and demonstrated that pathological invasive size correlated well with consolidation dimension, and moderately well with whole tumor dimension[90]; invasive size roughly approximated to tumor dimension in the mediastinal window plus 3mm[90]. However, Hattori and colleagues held an opposite view since their study showed that neither maximum tumor size nor solid component size was prognostic in part-solid lung cancer[91]. Along with the debate on tumor diameter, another indicator of tumor size, volumetric measurement, has also been

increasingly validated due to advances in radiologic technology[92,93]. To better address and unify the assessment of tumor size, the IASCL proposed the revised clinical staging algorithm for T category in part-solid nodules (Table 1.1)[94].

Table 1.1: Proposed clinical T descriptor of part-solid nodules by the IASCL.

CT image						
total tumor size (cm)	≤0.5	0.6-3.0	≤3.0	0.6-3.0	1.1-3.0	2.1-3.0
solid part (cm)	0	0	≤0.5	0.6-1.0	1.1-2.0	2.1-3.0
clinical stage		cTis	cT1mi	cT1a	cT1b	cT1c

AIS is classified as Tis; MIA is classified as T1mi.

(ii) Histological type

More than 80% of all lung cancers are NSCLC, among which adenocarcinoma is predominant and its incidence is rising steadily[17]. In an effort to better prognosticate lung adenocarcinoma beyond the use of the T component of the TNM staging classification, therefore, a new coding system was released by a multidisciplinary group (IASLC/ATS/ERS) in 2011[95]. In this new classification, adenocarcinoma is divided into three major groups based on the extension of tumor invasion: preinvasive lesions (atypical adenomatous hyperplasia and adenocarcinoma in situ [AIS]), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma. The latter group is further subdivided on the basis of the morphologic pattern of tumor cells: lepidic, acinar, papillary, micropapillary, and solid predominant adenocarcinoma[95]. These classifications showed a good inter-observer agreement[96] and correlated well with patient survival and disease recurrence, and these associations were independent of treatment modalities and TNM stage[97,98]. Therefore, the World Health Organization adopted this system in 2015[17].

As for squamous cell carcinoma (SCC), only a little progress has been made at the

histopathologcal level. The total number of SCC variants is cut down to 4 groups in the 2015 WHO classification[17]: keratinizing SCC, nonkeratinizing SCC, basaloid SCC, and preinvasive lesion (squamous cell carcinoma in situ). Nonkeratinizing SCC is a newly established subtype; however, this histologic subtyping seems of little clinically prognostic significance[99]. There is an ongoing need for additional studies to evaluate the clinical relevance of histopathologcal subtypes in SCC.

(iii) Grade and differentiation

Currently, there is no established histologic grading system for most lung cancers[17]. Usually, histologic grade is determined by the percentage of tumor differentiation and other features, such as specific growth patterns, cytological atypia, and mitotic rates (Table 1.2)[100]. Sun and colleagues, based on 5018 hospital- and 712 population-based cases, demonstrated that histologic grade was significantly associated with survival[100]. In addition, patients with less-differentiated carcinoma had a higher risk of recurrence than those with well differentiated carcinoma after resection, with a respective HR of 1.41, 1.71, and 1.83 for moderately-, poorly-, and undifferentiated carcinoma[100]. These findings were further confirmed by the study of von der Thusen and colleagues, in which the histological grade was defined by nuclear diameter and mitotic count[101].

Table 1.2: Possible components in tumor grading system

components	implications
nuclear atypia	survival, risk of recurrence
nuclear diameter	survival
mitotic index (count and rate)	survival
tumor budding	overall survival, risk of recurrence
architectural pattern	survival

For stage I adenocarcinoma, mitotic index has been shown to be an independent predictor for survival, with mean survival time of 8.9 years for tumors with up to 10

mitoses per 10 high-power fields compared to 5.2 years for tumors with more than 10 mitoses per 10 high-power fields[102]. In addition, tumor budding, defined as small tumor nests composed of less than five tumor cells, has been demonstrated to have prognostic significance in both adenocarcinoma and SCC[103,104].

1.1.3.2 Non-tumor related factors

(i) Age and sex

Patient's demographic characteristics play a significant role in lung cancer prognosis. It has been well acknowledged that chronological age is a negative predictor of various outcomes[105,106]. Undoubtedly, increasing age is associated with more comorbidities and higher risks of competing events, such as death from non-cancer diseases[107]. Eguchi and colleagues enrolled 2,186 patients with pathologic stage I NSCLC and found that both lung cancer-specific cumulative incidence of death and noncancer-specific incidence of death increased with patients getting older[105]. Postoperative complications are also more commonly seen in elderly patients receiving surgery for lung cancer[108]. In addition, older age is an independent predictor of poor quality of life[106]. Since the aging of the population is invreasing, more efforts should be dedicated to effective disease management in the elderly population, to improve their life expectancies as well as quality of life[109].

The association of gender with lung cancer survival has been widely reported, in which female sex has a consistently more favorable prognosis. A number of studies have demonstrated that women had better outcomes in terms of postoperative morbidities, 30-day mortality, long-term overall survival, and quality of life[110-112]. The mechanistic explanation underlying these observations has not been clearly elucidated yet, although premenopausal women were found to have a survival

advantage over postmenopausal women[113].

(ii) Body mass index

Being underweight has traditionally been regarded as a risk factor for major lung resection[114]. More currently, body mass index (BMI) has also been shown to correlate with patient survival[115,116]. Gupta and colleagues pooled 14 studies of lung cancer and observed, compared to patients with normal BMI (18.5–24.9 kg/m^2), a significantly lower lung cancer-related mortality in overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) patients, with a respective HR of 0.76 (95%CI, 0.68-0.85) and 0.68 (95%CI, 0.57-0.81)[115]. Dahlberg and colleagues pointed out a time dependence of obesity on survival; superior outcomes in obese patients were only noted in the early courses of cancer treatment (HR, 0.86; 95%CI, 0.75-0.99), after which (16 months from the date of treatment) they experienced increased hazard (HR, 1.54; 95%CI, 1.22-1.94)[116].

Dynamic change in body weight is also predictive. Early weight loss (>5% weight loss after baseline) has been identified as an indicator of worse survival (HR, 1.9; 95%CI, 1.10-3.19)[117], independent of traditional markers of prognosis. In contrast, patients with advanced lung cancer who had >5% weight gain during chemotherapy had significantly improved overall survival (HR, 0.54; 95%CI, 0.47-0.62)[118]. Besides implications for survival, weight loss is recognized as a negative prognostic factor of response to chemotherapy and quality of life[119].

(iii) Pulmonary comorbid disease

A growing number of studies have indicated that respiratory diseases do not only increase the risk of lung cancer development, but might also affect prognosis once

lung cancer has occurred. A recent population-based study revealed that pulmonary tuberculosis was an independent poor prognostic factor for lung cancer survival (HR, 2.36; 95%CI, 1.1-4.9)[120]. Similarly, Zhou and colleagues found that the presence of an old pulmonary tuberculosis lesion posed a 1.72-fold increased risk of mortality (95%CI, 1.12-2.64) in patients with squamous cell carcinoma[121]. However, on the contrary, concomitant active tuberculosis was reported to have the opposite effect, which prolonged survival in patients with advanced stage (III-IV) NSCLC[122]. There have been limited data on asthma in lung cancer. Brown and colleagues indicated that asthma increased risk of lung cancer death in non-smokers (RR, 3.54; 95%CI, 1.93-6.42)[123], whereas Vesterinen and colleagues described no survival difference in asthmatic and non-asthmatic lung cancer patients[124]. The presence of ILD significantly increased operative risk in patients receiving lung cancer resection, including postoperative acute respiratory distress syndrome and mortality[125]. Additionally, patients with lung cancer concomitant with ILD showed a higher risk of death, which is more likely due to cancer recurrence rather than the progression of ILD[126]. The impact of COPD and/or emphysema will be discussed in the next chapter. Interestingly, the contribution of coexisting pulmonary disease to lung cancer survival appeared to be gender-related[127,128]. The negative impact of tuberculosis, asthma, and/or COPD on lung cancer mortality was only observed among male patients in two recent studies from Taiwan[127,128].

1.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressive debilitating disease with an overall global prevalence of 10.1% in adults over the age of 40[129]. Alarmingly, it is now the third leading cause of death worldwide (around 5.6% of global death, Figure 1.5), after ischemic heart disease and stroke[130], and it substantially increases the burden on health care systems[131,132]. The

definition of COPD is still problematic, and the most acceptable one, as proposed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (2017), is 'a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases'[133]. Progressive dyspnea, chronic cough, and sputum production are the most frequent symptoms[134], while the diagnosis requires confirmatory spirometry demonstrating the presence of persistent airflow limitation: a ratio of post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of less than 0.7[134].

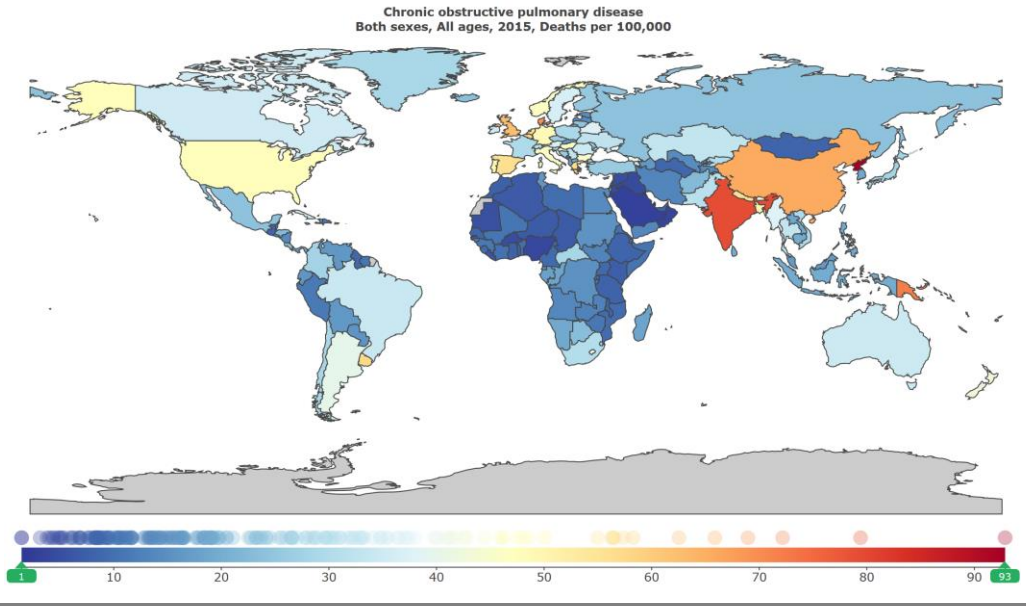


Figure 1.5: World map of the probability of death due to chronic obstructive pulmonary disease in all ages, by country. Institute for Health Metrics and Evaluation (IHME). Available from URL: http://vizhub.healthdata.org/gbd-compare/ (Accessed March 5, 2017).

1.2.1 Epidemiology

The prevalence of COPD is highly variable[135], ranging from 4.3% to 24.8%, which is possibly due to differences between geographic regions and methods for

establishing COPD diagnosis[129,132,136]. The rate is higher in South Africa (24.8%) but relatively lower in Asian countries, such as China (8.2%) and Japan (4.3%)[137,138]. In addition, several studies detected COPD based on pre-bronchodilator measurement[139,140]; it has been estimated that disease prevalence after use of a bronchodilator would be 27-52% lower than that without bronchodilation[141,142].

The U.S. National Health and Nutrition Examination survey showed that the overall age-adjusted prevalence of COPD was stable from 1988 through 2010, reaching about 14% of adults aged ≥20 years with an evidence of airflow obstruction (FEV_1/FVC <0.7)[143]. Additionally, the prevalence estimate is much higher in older age groups[144]. Males were historically considered to be more susceptible to development of COPD, attributed to the gender-specific patterns of tobacco and occupational exposures[145,146]. Nevertheless, a significant shift in gender prevalence towards higher rates in females has been noted in several recent epidemiological investigations[147,148]. As to socioeconomic status, COPD is more prevalent among those who are in poverty and have no educational qualifications[149,150].

The accurate estimate of COPD prevalence, as alluded to earlier, depends largely on a correct diagnosis of COPD. However, COPD is commonly misdiagnosed in the primary care setting, which consists of both underdiagnosis (not diagnosing COPD in patients with evident airflow limitation), and over-diagnosis (diagnosing COPD in someone who does not have it).

1.2.1.1 Underdiagnosis of COPD

Although individuals with COPD can suffer from relentless respiratory symptoms, many individuals may not recognize their symptoms as being due to a disease, because shortness of breath or exertional dyspnea may be attributable to aging, while cough

and sputum production may be considered a consequence of smoking[151]. Moreover, even if these patients are able to visit their primary care doctors during the onset of the signs of COPD, doctors often fail to recognize the significance of symptoms as well[152,153]. Hence, a high rate of underdiagnosis would be anticipated. It has been estimated that 60-85% of patients, mainly with mild to moderate disease, have not been diagnosed in the general population[154,155]. Patients with undiagnosed COPD miss valuable opportunities to retard disease progression through optimal management, placing them at substantial risk of poorer health status[156,157], which in turn contributes to a great extent to the health care burden[131]. Predictors for an undiagnosed COPD include male sex, younger age, lower education level, and being of racial/ethnic minority[155,156]. A COPD-like respiratory exacerbation event may act as a trigger for physician to consider the diagnosis of COPD.

1.2.1.2 Over-diagnosis of COPD

Over-diagnosis is also frequent, with a reported rate ranging from 25.8% to 42.5% across different countries[158,159]. A recent population-based longitudinal cohort study has shown that over-diagnosed but not undiagnosed COPD seems to place significant burden on the health care system[160]. It is because over-diagnosis of COPD will inevitably lead to over-treatment, which may be detrimental to the patient due to the side effects associated with medications[161]. Pre-bronchodilator spirometry use, improper spirometry technique, and incorrect interpretation of the results appeared to contribute to over-diagnosis in clinical practice[162,163], and training in spirometry holds the promise of improving the accuracy of identification of COPD[162]. From a patient's perspective, overweight and obese subjects are prone to be given a misdiagnosis of COPD[164,165]. Therefore, health-care professions should be aware that respiratory health (symptom and function) is linked to an individual's weight, and thus

an alternative diagnosis for respiratory symptoms ought to be entertained and treatment should be adjusted accordingly[166].

1.2.2 Severity and phenotypes

Historically, the classification of COPD was based solely on FEV_1. Nowadays, the use of spirometry results alone has been realized insufficient to characterize COPD, as COPD is a complex syndrome with numerous pulmonary and extra-pulmonary components[167]. In 2013, the GOLD recommendations proposed two additional parameters for the assessment of COPD, i.e. symptoms and exacerbations[134]. Symptom evaluation is based on either the Modified British Medical Research Council (mMRC) questionnaire[168] or the COPD Assessment Test (CAT)[169], where mMRC assesses merely the impact of dyspnea whereas CAT provides a border health status assessment (covering both respiratory and systemic symptoms). The cut-off points are 2 and 10 for mMRC and CAT, respectively, with a higher score indicating a high level of symptoms. An exacerbation is defined as a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[134], with a history of ≥2 exacerbations in the preceding year indicating high risk. Thus, patients are classified as A, B, C, D depending on the combination of these three parameters (Figure 1.6). However, subsequent analyses have revealed that the GOLD quadrant classification does not seem to perform any better than spirometric grades (FEV_1 alone) in predicting mortality and other serious health outcomes[170-172]. In addition, physicians are often confused about the classification of risk dimension because patients may present different degrees of airflow limitation and exacerbation history. Therefore, the GOLD 2017 guideline has tried to revise the ABCD classification, separating spirometric grades from the ABCD grouping (Figure 1.6). Further classification systems are also needed to address this issue.

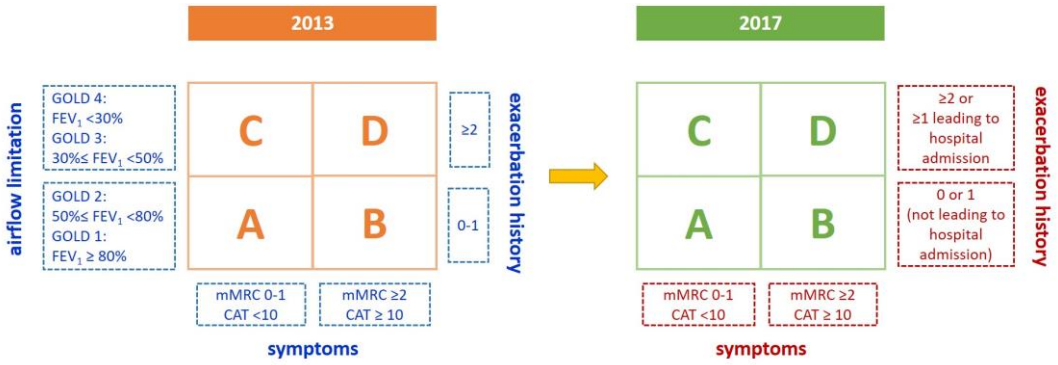


Figure 1.6: GLOD 2013 and 2017 classifications. If there is a discrepancy between the risk category as assessed by spirometric classification and that derived from exacerbation history, the assessment pointing to the highest risk should be used.

1.2.2.1 Severity

COPD severity refers to the extent of functional loss of the target organ(s) that eventually impacts on prognosis[173], which has traditionally been determined by the degree of airflow limitation measured by FEV_1[134]. In recent years, however, it is increasingly recognized that FEV_1 by itself does not adequately describe disease severity, and that its role in predicting disease progression is also limited in some circumstances such as during hospitalization[174]. Therefore, a comprehensive assessment using a multicomponent index is largely being advocated to refine prognostication. The best well known indices are BODE, ADO, and DOSE (Table 1.3), among which the BODE index serves as the benchmark that lays the groundwork for further risk stratification projects.

(i) *BODE*. The BODE index integrates four variables due to their strong associations with 1 year mortality in COPD patients[175]. The index has been regarded as one of the most effective multidimensional grading systems as it captures various domains of COPD: degree of pulmonary impairment (FEV_1), patient's perception of symptoms (the mMRC dyspnea scale), as well as systemic consequences of COPD (6-

min walk distance [6MWD] and BMI)[175]. The total score of the BODE index ranges from 0 to 10 points, with higher scores indicating a greater risk of death. In terms of predictive ability, the BODE index has been demonstrated to perform better than FEV_1 alone at predicting the risk of death from all causes and from respiratory causes among patients with COPD[175]. Moreover, the BODE index also provides valuable prognostic information with regard to quality of life, exacerbation and hospitalization, and patient's willingness to participate in a rehabilitation programme[176-179].

Table 1.3 Composite scores for assessing COPD severity

variable	points			
	0	1	2	3
BODE[175]				
FEV_1 (% of predicted)	≥65	50-64	36-49	≤35
distance walked in 6 min (m)	≥350	250-349	150-249	≤149
mMRC dyspnea scale	0-1	2	3	4
body mass index (kg/m^2)	>21	≤21		
mBODE[180]				
peak oxygen uptake* (ml/min/kg)	>25	20-25	15-20	<15
or (% of predicted)	>70	60-69	40-59	<40
eBODE¶ and BODEx§ indices[181]				
frequency of severe exacerbations	0	1-2	≥3	
ADO[182]				
FEV_1 (% of predicted)	≥65	36-64	≤35	
mMRC dyspnea scale	0-1	2	3	4
age※ (years)	40-49	50-59	60-69	70-79
DOSE[183]				
mMRC dyspnea scale	0-1	2	3	4
FEV_1 (% of predicted)	≥50	30-49	<30	
smoking status	nonsmoker	smoker		
exacerbations per year	0-1	2-3	>3	

*peak oxygen uptake replacing distance walked in 6 min in BODE index; ¶adding frequency of severe exacerbations into BODE index; §frequency of severe exacerbations replacing distance walked in 6 min in BODE index; ※score 4, age 80-89; score 5, age ≥90.

(ii) *mBODE, eBODE, and BODEx*. These indices are derived from BODE index. The

mBODE index replaced the 6MWD with peak oxygen uptake (VO_{2peak}) as a measurement of exercise capacity, for the reason that VO_{2peak} is considered an objective test, and it can reflect the physiologic response during effort, while 6MWD depends mostly on individual motivation[180]. Similarly, eBODE and BODEx take into consideration the frequency of severe exacerbations requiring hospital management in one year[181]. All the three modified indices show a comparable predictive ability as the conventional BODE index in terms of all-cause mortality[181,184].

(iii) *ADO and DOSE*. Both indices are introduced to lend support the prognostic assessment of COPD patients in different clinical settings. The ADO index is used to estimate 3-year risk of mortality in patients with more severe COPD, and it showed improved predictive value compared to the BODE index[182]. DOSE further progresses the prognostic tool from mortality to health-related outcomes. It is a stronger predictor of future hospital admission and is also related to the number of exacerbations in the subsequent year[183].

These multicomponent grading systems have been shown to better reflect COPD severity and predict patient's outcomes than FEV_1 alone; however, whether such prognostic information can aid clinicians in the choice of therapy, and improve patient prognosis, is not yet clear. Therefore, further studies are desirable to validate the clinical utility of these prognostic indices in terms of resources allocation and treatment assignment.

1.2.2.2 Phenotypes

At the individual level, phenotype is derived from genotype and refers to the observable structural and functional characteristics of an organism[185]. Nowadays, the concept of phenotype is embedded in the clinical setting, and COPD phenotype is used

to depict ‘a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, rate of disease progression, or death’[186]. Therefore, the goal of phenotyping, from the clinical point of view, is to characterize the homogeneous features of clinical presentation and disease progression that are shared within a distinct group of individuals, and then provide them with the best health care in order to achieve better clinical results[187]. Therefore, in contrast to the severity, a clinical phenotype captures a wider range of disease characteristics and has both prognostic and therapeutic implications.

Although there is still little agreement as to the total number of COPD phenotypes, several phenotypes are generally agreed upon. One of the most well-identified phenotypes is α-1 antitrypsin deficiency (AATD), which is an inherited genetic disorder determined by the α1AT gene on chromosome 14q32.1[188]. The exact prevalence of AATD in patients with COPD is unknown because it is frequently under-recognized by clinicians[189], with an estimated delay between first symptom and initial diagnosis of 7.2 to 8.3 years[190]. The AATD phenotype is characterized by an early onset of emphysema with a basal predominance and positive response to intravenous augmentation therapy (i.e., the infusion of purified pooled human plasma α-1 antitrypsin)[191].

The second validated phenotype is emphysema-hyperinflation phenotype. Pulmonary emphysema is defined, in pathological terms, as the abnormal permanent enlargement of the airspaces distal to the terminal bronchioles[192]. The destruction of bronchiolar walls contributes to the difficulty in alveolar emptying, originating air trapping and hyperinflation. This phenotype is featured by upper lobe emphysema, significant dyspnea, and intolerance to exercise[151,193,194], and is seen more frequently in patients of older age, male sex, and lower BMI[195,196]. Compared to other phenotypes, the emphysema-hyperinflation phenotype appears to respond best to lung volume

reduction surgery, with a significant improvement in survival and functional outcomes[197,198]. The presence of hyperinflation has also been regarded as a reliable predictor of the response to bronchodilators[199]. On the other hand, anti-inflammatory treatment seems not to be indicated in this phenotype during periods of stability, because it failed to demonstrate any benefit on pulmonary function and exacerbation rates[200,201].

The third common phenotype is chronic bronchitis phenotype. It is classically defined as habitual cough and sputum production for 3 months in a year for a period of 2 consecutive years[202]. Appropriately 11.5-24.5% patients with COPD are found to have a chronic bronchitis phenotype[203,204], and patients are more likely to be younger, male gender, Caucasian race, and current smokers[204,205]. Radiological increased airway wall thickness is an indication of chronic bronchitis. This phenotype is also reportedly associated with multiple clinical consequences, including greater symptom burden (dyspnea and sputum), higher risk of exacerbations and worse quality of life[202,205,206]. Therefore, treatment aimed at increasing mucus clearance and reducing exacerbations may be crucial in these patients[207].

The COPD-asthma overlap syndrome has been increasingly recognized as a particular phenotype due to its distinct manifestations and treatment in the clinical setting[208]. The estimated prevalence ranges from 23% to 38% of COPD patients, being 31.5% when using the bronchodilator test as a reference[154,187]. The accepted definition for this mixed phenotype is an airflow obstruction that is not completely reversible, along with signs of increased obstruction reversibility (Table 1.4)[208]. Personal history of asthma and/or atopy, less intense smoking exposure, sputum and/or peripheral eosinophilia, high concentration of exhaled nitric oxide, positive prick test, and reversibility in the bronchodilator test suggest a diagnosis of COPD-asthma overlap syndrome[187,209]. In addition, patients with overlap phenotype seem to have more concomitant wheezing compared to those with COPD only[210]. With respect to

differential treatment, the COPD-asthma overlap phenotype demonstrates a good response to inhaled corticosteroids at the level of lung function and symptom relief, while the benefit of anti-inflammatory treatment is only marginal in patients with COPD alone who do not present the aforementioned characteristics[211,212].

Table 1.4: Clinical characteristics of COPD, asthma, and COPD-asthma overlap phenotype

	healthy	asthma	mixed phenotype	COPD
symptoms	absence	presence	presence	presence
FEV_1/FVC	≥70%	≥70%	<70%	<70%
FEV_1% predicted	>80%	>80%	<80%	<80%
airway hyper-responsiveness[#]	>12 ml	<12 ml	<12 ml	>12 ml

[#]provocation dose of hypertonic saline that induces a 15% fall in FEV_1. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

The frequent exacerbator phenotype, defined as 2 or more exacerbations per year with at least 4 to 6 weeks interval between these exacerbations[213,214], which causes an enormous burden on the health care systems[187], has gained significant attention in recent years. Exacerbator patients have without doubt poor lung function and quality of life[215,216], and patients who do not completely recover from an exacerbation may have an average of 8ml/year more deterioration in FEV_1[215]. Although patient gender, smoking history, COPD duration and severity are predictive of frequent exacerbations[217], history of previous exacerbations has been demonstrated to be the single risk determinant across all GOLD stages[213,218]. The treatment of choice includes long-acting bronchodilators and anti-inflammatory agents, both of which have been shown to reduce the frequency of exacerbations[219,220]. The use of antibiotics is also suggested during stable phases, particularly for patients with purulent sputum, without showing a significant increase in bacterial resistances[221,222].

Other possible phenotypes have been proposed, but are not fully validated against clinical outcomes and best treatment assignments. A phenotype of fast lung function decline has been described, with an annual decline in FEV_1 by around 40ml to 60ml,

which seems strongly associated with current smoking[223,224]. However, the diagnosis can only be made after close monitoring of lung function for at least 3 years, and no modifiable treatment has been identified for this type of patient; thus, it is of little clinical significance. A COPD-bronchiectasis clinical phenotype has also been suggested[225], since radiologic bronchiectatic change has been shown to exert a negative impact on overall prognosis of COPD, including airway obstruction, exacerbations, and all-cause mortality[226,227]. Still, it is debatable whether it is a comorbid association or clinically relevant phenotype. In addition to the aforementioned, phenotypes of mild airway obstruction but disproportionately severe dyspnea[228], severe pulmonary hypertension disproportionate to the underlying COPD[229], non-exacerbator[230], and a phenotype with persistent inflammation[231] have been reported. It should be noted that any phenotype may have different underlying mechanisms and that any one individual may manifest multiple phenotypes.

Accordingly, pharmacologic therapy should be tailored to specific phenotype during the multidimensional assessment of COPD. A phenotype-based therapeutic approach was proposed by Miravitlles and colleagues[232] based on the currently available evidence (Figure 1.7), in order to maximize the scope of therapy while limiting unnecessary use of drugs. Comprehensive intervention is the cornerstone of the management of COPD, and bronchodilators are the basis of treatment of COPD irrespective of the clinical phenotype. Inhaled corticosteroids are indicated in all phenotypes except for non-exacerbator. Patients with chronic bronchitis phenotype are the only candidates to receive phosphodiesterase-4 inhibitors. These indications offer a pragmatic and achievable approach to the management of the complexity implicit to this disease. However, further investigation is still warranted to justify the phenotyping. From a clinical perspective, validation from independent cohorts should be conducted to test the reliability and discriminative ability and then to refine the phenotypic group for each of the outcomes of interest. From a research standpoint, mechanistic studies are needed to understand the biologic and physiologic basis for

the shared clinical features within any distinct phenotype.

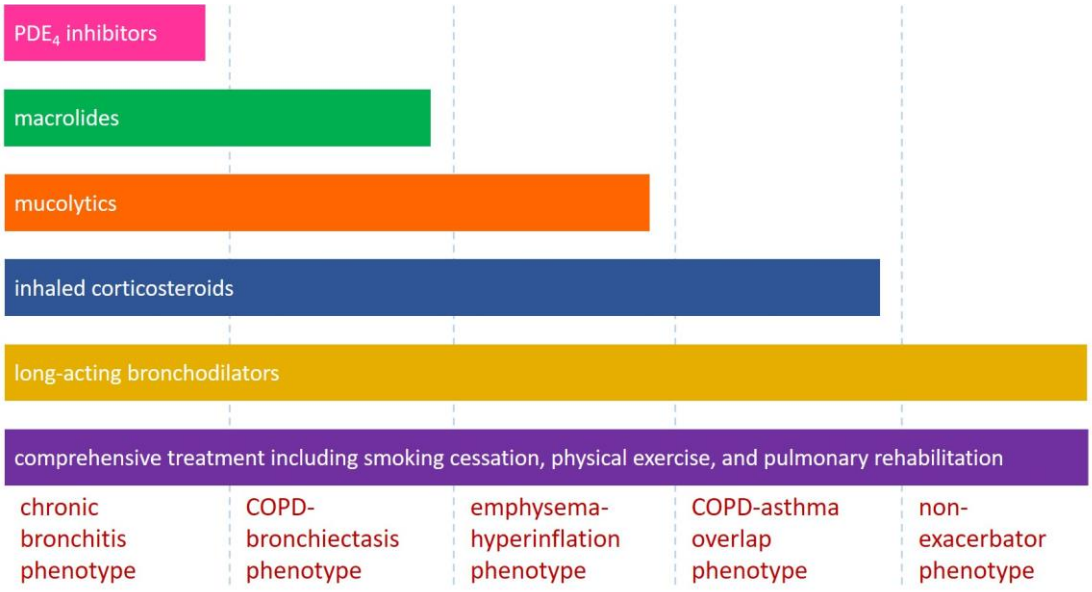


Figure 1.7: Proposed pharmacological treatment of COPD according to clinical phenotypes. COPD: chronic obstructive pulmonary disease; PDE_4: phosphodiesterase-4.

Note: the order of the bars does not represent the order of preference for treatment.

1.2.3 Comorbid diseases

Though smoking and aging may lead to comorbidities, it is increasingly recognized that patients with COPD also have a high burden of concurrent diseases which may be independent of the two known major risk factors. Data from epidemiological studies have shown that COPD is frequently associated with comorbidities, with an average number of 3.7 comorbid diseases compared with 1.8 in healthy controls[233]. It is estimated that 84 to 97.7% of individuals with COPD have at least one comorbid condition[234-237], 68.8 to 83.6% have at least two[238,239], and 46.5 to 72.9% have three or more[234,237-239], with the most serious and prevalent being cardiovascular diseases, lung cancer, metabolic disorders, and cognitive and psychological impairment[167,240]. It is still uncertain whether the frequency of comorbidities increases with COPD progression[241,242], however. Several concomitant diseases have been reportedly

associated with an early or late COPD; for example, diabetes, hypertension, and dyslipidemia are frequently described in advanced COPD[243-245] while lung cancer and chronic kidney disease are more commonly seen in mild to moderate COPD[246-248]. Figure 1.8 displays the major comorbidities in COPD and their prevalence[244,249,250].

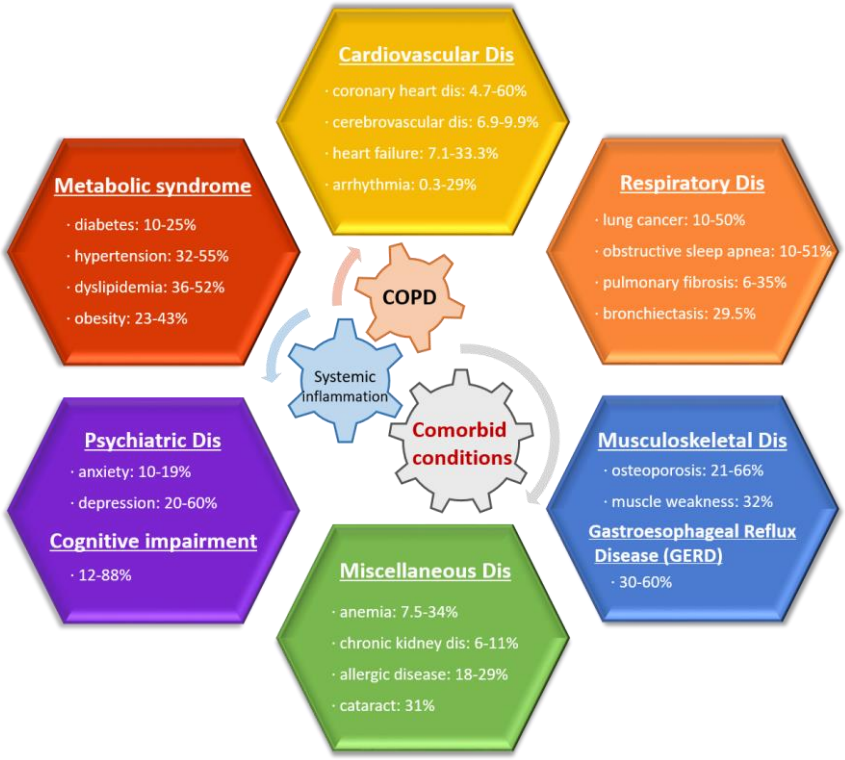


Figure 1.8: Comorbidities of COPD and their prevalence. COPD: chronic obstructive pulmonary disease.

The association of comorbidities with specific COPD phenotypes has also been sporadically reported[251], where patients with emphysema phenotype had a greater prevalence of pulmonary heart disease and cachexia[252]; patients with chronic bronchitis phenotype had a higher risk of obesity, diabetes, and gastroesophageal reflux disease (GERD)[205,252,253]; and patients with asthma/COPD overlap phenotype were more likely to have arthritis, stroke, and other respiratory diagnoses (pulmonary tuberculosis, bronchiectasis, and sleep apnea)[254]. Patients with frequent exacerbator phenotype are reported to be susceptible to psychiatric disorders, namely anxiety and depression[255]. The comorbid GERD seems to be specifically associated with chronic

bronchitis phenotype in COPD[205], and this phenotype of patients showed a higher concentration of cardiovascular risk factors[195].

Beyond establishing the prevalence and characteristics of comorbidities in COPD, there have been a great number of studies that have attempted to understand the general contribution of comorbidities to COPD outcomes. Accumulating evidence has indicated a nearly ubiquitous negative impact of comorbidities in the COPD population, which increases healthcare utilization, reduces health-related quality of life, and complicates the management of COPD[250,256,257]. Almagro and colleagues studied hospitalized patients with a COPD exacerbation, and found that comorbidity was related to the length of stay and hospital readmission for both COPD and other causes, independent of age, sex and severity of airflow obstruction[258]. In addition, the excess healthcare expenditure in COPD was associated with overall comorbidity burden[259,260] as well as some specific comorbidities, such as hypertension, congestive heart failure, mild liver disease, diabetes and anemia[261-263].

The relationship between the increasing number of comorbidities and the deterioration in quality of life has been well demonstrated in 4 large epidemiologic studies[239,264-266] and 1 recent systemic review[267]. Meanwhile, several studies have found that some prevalent comorbidities were individually associated with a significant decline in health status, including heart failure, arthritis, urinary incontinence/prostatic disease, diabetes, osteoporosis, anemia, and psychiatric disorders (depression and anxiety)[239,268-270]. Furthermore, the presence of comorbidities also poses a challenge for the effective management of COPD. For example, heart failure and abnormal obesity may obscure the diagnosis of COPD by preventing accurate assessment of airflow limitation[271]. Pharmacological treatment also becomes more complex, as some agents that are viewed as the cornerstone of the treatment for comorbidities might have some risks in COPD patients (e.g. β-blockers for congestive heart failure might affect COPD with asthmatic component),

and vice versa (e.g. systemic steroids for COPD exacerbations might worsen coexistent diabetes, hypertension, and/or osteoporosis)[272].

Therefore, defining the nature of the association between COPD and other chronic conditions is of prime importance to improve the health status of COPD patients through the timely detection, accurate assessment and optimal care of comorbidities.

1.2.3.1 Assessment of comorbidities in COPD

There are a number of approaches to assessing comorbidities in COPD patients, including Charlson Comorbidity Index (CCI), COmorbidity TEst (COTE), and COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index, which are designed for the description of comorbidity burden in COPD specifically (Table 1.5). Other studies have attempted to incorporate comorbidities into a multi-dimensional assessment tool for COPD, such as Comorbidity, airway Obstruction, Dyspnea, and previous Exacerbation (CODEX) index, Dyspnea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation (DECAF) score, and Comorbidome (Table 1.6). The selection of index depends largely upon the outcome of interest.

(i) *Charlson comorbidity index (CCI)*. This is a general index and probably the most extensively used tool for assessing the impact of comorbid diseases on overall survival[273]. CCI was proposed for the first time in 1987, and encompasses 19 chronic diseases which were assigned point scores corresponding to their risks of mortality[273]. Although CCI was not developed using COPD patients (it was based upon 685 patients with primary carcinoma of the breast), it could also provide some clinical and prognostic information in regard to healthcare utilization and mortality after discharge. in patients hospitalized for an acute exacerbation of COPD[258,261,274]. Patients having a CCI score of 3 or more were at 2.2-fold increased risk of death as compared to those

with a lower burden of comorbidities[274].

Table 1.5: Assessment of comorbid diseases in patients with COPD

scales	the spectrum of comorbidities	predictive value
CCI[273]	metastatic solid tumor, acquired immune deficiency syndrome (6 points); moderate or severe liver disease (3 points); hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma (2 points); myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes (1 point)	all-cause mortality[274]; healthcare utilization and medication costs[261]
COTE[275]	lung, esophageal, pancreatic, and breast[#] cancer, anxiety[#] (6 points); all other cancer, liver cirrhosis, atrial fibrillation/flutter, diabetes with neuropathy, pulmonary fibrosis (2 points); congestive heart failure, gastric/duodenal ulcers, coronary artery disease (1 point)	COPD specific mortality[275]
COMCOLD[269]	depression (6 points); anxiety (4 points); peripheral artery disease (3 points); cerebrovascular disease (defined cerebrovascular accident or transient ischemic attack, 3 points); symptomatic heart disease (defined as coronary heart disease and/or heart failure, 3 points)	health status[269]

[#]valid on the female population only. CCI: Charlson comorbidity index; COTE: COPD specific comorbidity test; COMCOLD: Comorbidities in chronic obstructive lung disease.

(ii) *COPD specific comorbidity test (COTE)*. The COTE index, the first COPD-specific index that predicts the mortality risk associated with comorbidities accompanying COPD, was proposed by Divo and colleagues in 2012[275]. The index was constructed based on 12 easily identifiable comorbidities that exhibited significant association with mortality, and each comorbidity was given a point score in proportion to their hazard ratios[275]. Patients with a higher COTE index had an increased risk of death from both causes related to COPD (HR, 1.13; 95%CI, 1.08-1.18) and causes other than COPD (HR, 1.18; 95%CI, 1.15-1.21)[275], and a COTE score greater than or equal to 4 points increased by 2.2-fold the risk of death[275]. With respective to prognostication, the

behaviour of the COTE index to predict mortality was similar to that of the Charlson index but with the advantage of being simpler to construct[256,276]. Additionally, adding the COTE to the BODE index could significantly improve outcome prediction[277].

Table 1.6: Multi-dimensional prognostic tool for comorbidities accompanying COPD

index	description	prognostic ability
CODEX[278]	comorbidity (Charlson index): 0-4 [0], 5-7 [1], ≥8 [2]; obstruction (FEV_1%): ≥65 [0], 50-64 [1], 36-49 [2], ≤35 [3]; dyspnea (mMRC scale): 0-1 [0], 2 [1], 3 [2], 4 [3]; exacerbation (hospitalization): 0 [0], 1-2 [1], ≥3 [2].	mortality and hospital readmission in the short (3m) and medium term (12m) after discharge
DECAF[279]	dyspnea (eMRCD): eMRCD 5a [1], eMRCD 5b [2]; eosinopenia: $<0.05\times10^9$/L [1]; consolidation (chest radiography): presence [1]; acidemia: pH<7.3 [1]; atrial fibrillation (ECG): presence [1].	in-hospital mortality in patients hospitalized for acute exacerbations of COPD
comorbidome[280]	age, number of hospital admissions in the previous year, dyspnea (mMRC), functional status (Katz index), chronic home oxygen therapy, and comorbidities (ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic kidney disease, depression, and atrial fibrillation).	mortality at 3 months in hospitalized COPD patients

The number in brackets represents the assigned point score.
CODEX: Comorbidity, airway obstruction, dyspnea, and previous exacerbation; DECAF: Dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation.

(iii) *Comorbidities in chronic obstructive lung disease (COMCOLD)*. The COMCOLD index was developed in 2014 to evaluate the collective impact of comorbidities on patient-reported health status[269], as measured by the Feeling Thermometer – a modified visual analogue scale ranging from 0 (dead) to 100 (perfect health)[281,282]. After adjusting for FEV_1% predicted, 5 prevalent comorbidities (with prevalence >5%) were identified to contribute to the poor health status in patients with COPD, and then point scores were assigned to each comorbidity, with higher score indicating worse health outcome. Therefore, the COMCOLD index complements the existing

comorbidity indices that predict death, which can help clinicians to identify patients who may suffer from a decreased health status, and therefore to prioritize treatment opinions[269].

(iv) *Comorbidity, airway obstruction, dyspnea, and previous exacerbation (CODEX)*. The CODEX index was proposed by Almagro and colleagues in 2014, with the principal aim to predict mortality and hospital readmission for 3 to 12 months after discharge in patients hospitalized for COPD exacerbations[278]. It is based on 4 parameters, comorbidity, obstruction, dyspnea, and previous severe exacerbations, in which comorbidity was measured using the age-adjusted CCI[283], whereas the remaining 3 variables were evaluated as described for BODEX thresholds[181]. The original Charlson index was stratified in tertiles (0-4, 5-7, and ≥8) in the CODEX index, and a corresponding score point (0, 1, and 2) was allocated. When compared with other existing indices, the CODEX index had a significant better predictive capacity in terms of death and/or re-hospitalization at 3 months and 1 year after discharge than BODEX (BMI, airflow obstruction, dyspnea, and previous severe exacerbations)[181], DOES (dyspnea, airflow obstruction, smoking status, and exacerbation frequency)[183], and ADO (age, dyspnea, and airflow obstruction) instruments[182].

(v) *Dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation (DECAF)*. The DECAF score is the first index that incorporates both clinical and laboratory information, to predict in-hospital mortality in patients hospitalized with an exacerbation of COPD[279]. For pragmatic reasons, the 5 strongest predictors of mortality were selected to form the index, and point scores for each predictor were assigned according to the regression coefficient. The DECAF index showed excellent discrimination with an area under the receiver operator characteristic curve of 0.86, and performed significantly better for the prediction of in-hospital mortality than other prediction tools[279,284], including the Acute Physiology and Chronic Health Evaluation II prognostic index[285], the COPD and Asthma Physiology Score[286], and the

BAP-65[287], which have all been proposed as useful predictive instruments in acute exacerbations of COPD. The superior performance of DECAF is of prime importance for patients deemed at low risk (score 0-1), who may be considered suitable for home treatment[284].

(vi) *Comorbidome*. The COPD comorbidome is a graphic expression of the relationship between comorbidities and COPD that resembles the solar system, where the area of the circle relates to the prevalence of the diseases, and the proximity to the center (mortality) expresses the strength of the association between the diseases and risk of death (Figure 1.9)[288].

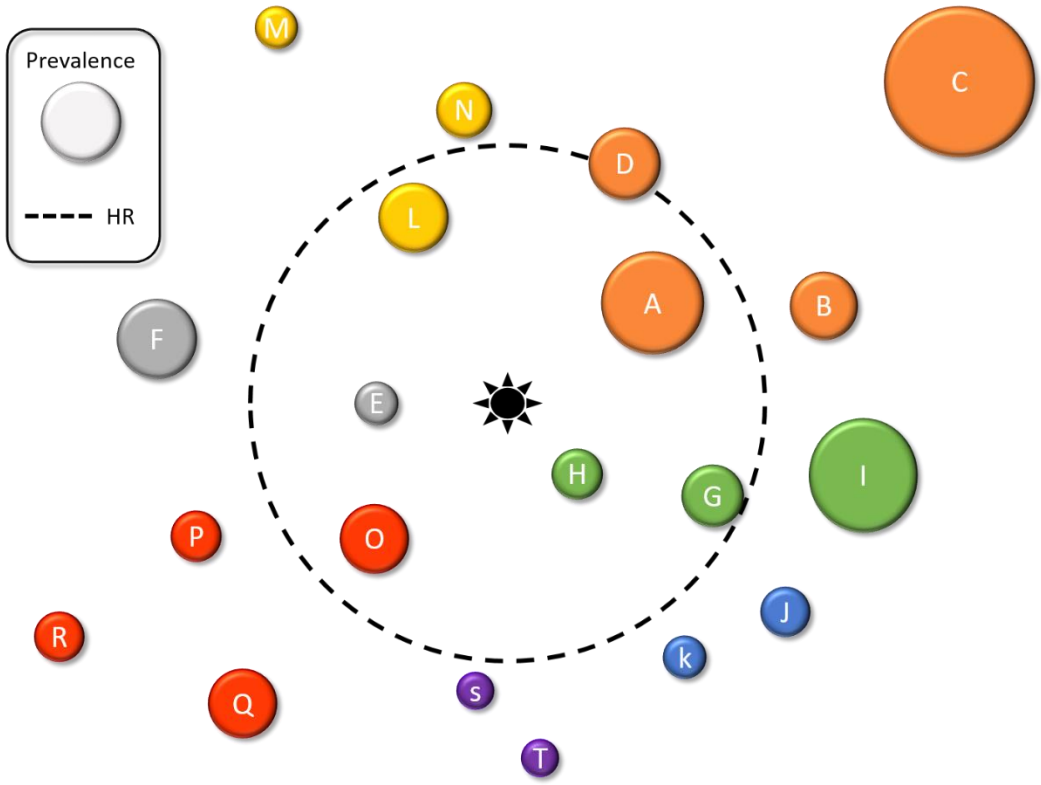


Figure 1.9 Comorbidome solar system. Each 'planet' represents one comorbid disease. The area of the circle relates to the prevalence of the disease, while the proximity to the 'sun' expresses the strength of the association between the disease and risk of death. Bubble colors represent organ systems.

It was initially created by Divo and colleagues[275] based on the BODE cohort, which enrolled clinically stable COPD outpatients with relatively few comorbidities[175]. In

order to verify and expand its applicability, Almagro and colleagues subsequently replicated the comorbidome in patients who were hospitalized for COPD exacerbation for the assessment of mortality at 3 months after discharge[280]. Comorbid conditions were collected via the Charlson index, with other relevant chronic diseases identified using a specific questionnaire. Additionally, data on dyspnea, functional status, and previous hospitalizations for COPD or other causes were analyzed. Finally, a new comorbidome was developed encompassing different parameters from that previously published by Divo and colleagues[275], reflecting the distinct pattern and influence of comorbidities in different COPD patient population.

These multi-dimensional indices could help unravel the overall burden of COPD-related comorbidities, assist in the assessment and prognosis of various outcomes in COPD, and advance our understanding of the systemic manifestations and extra pulmonary effect of COPD.

1.2.3.2 Current challenges and future efforts

As aforementioned, comorbidities have a considerably detrimental impact on the overall prognosis in patients with COPD. The negative impact is exacerbated because some comorbidities, such as depression and osteoporosis, are still substantially underdiagnosed and/or undertreated in the majority of COPD patients[250,289]. A screening strategy for comorbidities has not been established so far. In this regard, for instance, Negewo and colleagues recommended timely diagnosis of all COPD-associated comorbidities during the assessment of pulmonary condition[256]. Smith and colleagues argued that screening protocols should be limited to comorbidities that are prevalent, have effective therapeutic options, and alter prognosis significantly[249], and they proposed a checklist to assist the clinicians in screening for comorbidities in the outpatient setting (Table 1.7). The checklist is grouped by organ systems, including

cardiovascular system, pulmonary pathology, mental health, metabolic disease, chronic kidney disease, and gastroenterology[249].

Table 1.7: Checklist for screening COPD-associated comorbidities.

Cardiovascular system	Pulmonary pathology	Metabolic disease
☐ hypertension	☐ pulmonary hypertension	☐ hyperlipidemia
☐ atrial fibrillation	☐ lung cancer	☐ diabetes
☐ ischemic heart disease	☐ pulmonary fibrosis	☐ osteoporosis
☐ heart failure	☐ pulmonary embolism	☐ obesity
Mental health	**Gastroenterology**	**Urology**
☐ anxiety	☐ GERD	☐ chronic kidney disease
☐ depression	☐ peptic ulcer disease	

GERD: gastroesophageal reflux disease. Data from Smith MC, et al. Int J Chron Obstruct Pulmon Dis. 2014;9:871-888.

In addition to screening, current management strategies largely fail to provide clear recommendations to address these complex comorbid diseases in the presence of COPD, although the importance of integrating comorbidities in the assessment and treatment of COPD is gradually being recognized[290]. Agusti and colleagues proposed the 'COPD control panel' as a disease management model[291]. The control panel considers three domains of the disease: severity (FEV_1, inspiratory to total lung capacity ratio [IC/TLC], arterial oxygen pressure [PaO_2], 6-min walk distance [6MWD], and number of comorbidities), activity (smoking, FEV_1 decline, frequency of exacerbations, weight, and inflammatory biomarkers), and impact (mMRC, CAT, and daily activity), to guide clinician to assess and manage patients with COPD more comprehensively[291]. Vishnivetsky and colleagues subsequently pointed out that the 'COPD control panel' should place more emphasis on comorbidities[292] since comorbidities are the second most prevalent sign of COPD after non-reversible obstruction in real-life COPD patients[236]. Similarly, the chronic care model[289] and inflammometry, multidimensional assessment, and case management approach[293] have been recently proposed, providing some practical interventions as to integrated care for COPD patients. Nevertheless, it has to be admitted that these suggestions are

largely based on expert opinion. Therefore, there is still an ongoing need to explore more efficient screening strategies and optimal tailored interventions in the management of comorbid patients with COPD in large-scale studies, which could help to maximize efficacy, limit cost, and ultimately improve patient clinical outcomes.

CHAPTER TWO

ASSOCIATION BETWEEN LUNG CANCER AND COPD

2.1 Clinical Association between Lung Cancer and COPD

COPD and lung cancer have attracted substantial attention over the past few decades due to the potential links between these two diseases and their combined mortality burden on healthcare system worldwide[294,295]. Recent systematic research from the Global Burden of Disease Study shows that both COPD and lung cancer are among the top ten causes of years of life lost in 2013[294], and they are projected to rank fourth and sixth cause of death in the next decades, respectively[295]. COPD is generally defined as chronic minimally reversible airflow obstruction on the basis of spirometry (post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] less than 70%[134]), but it has now been recognized as a heterogeneous group of diseases, encompassing two well-characterized phenotypes: chronic bronchitis and emphysema[134].

Although many previous studies have investigated the role of COPD in the development and prognosis of lung cancer, their conflicting results have not been clearly understood, and some burgeoning areas of research, such as the incorporation of COPD into lung cancer screening criteria, still remain as a forum of open discussion (Figure 2.1).

2.1.1 COPD and lung cancer risk

Numerous studies have demonstrated the presence of COPD *per se* to be an independent risk factor for lung cancer[296]. Evidence on the first epidemiologic association between lung cancer and COPD can be traced back to the 1980's when Skillrud and Tockman revealed a four-fold increase in lung cancer incidence in patients with COPD[247,297]. Since then, this association has been extensively observed in population-based studies[298,299], lung cancer screening trials[300-302], and case-control

studies[296,303-305]. However, with the widespread use of computed tomography (CT), the research on the etiologic association has been gradually changing from spirometry-defined COPD to CT-diagnosed emphysema[306]. This has led to controversy about whether airflow obstruction on spirometry, or emphysema on CT scan, is the more important manifestation of COPD linked to an increased risk of lung cancer. Several studies[298-300,303,304,307-309] have investigated the interaction between airflow obstruction and emphysema relative to lung cancer risk, but their results are still contradictory (Table 2.1). Reasons for these disparities may be threefold.

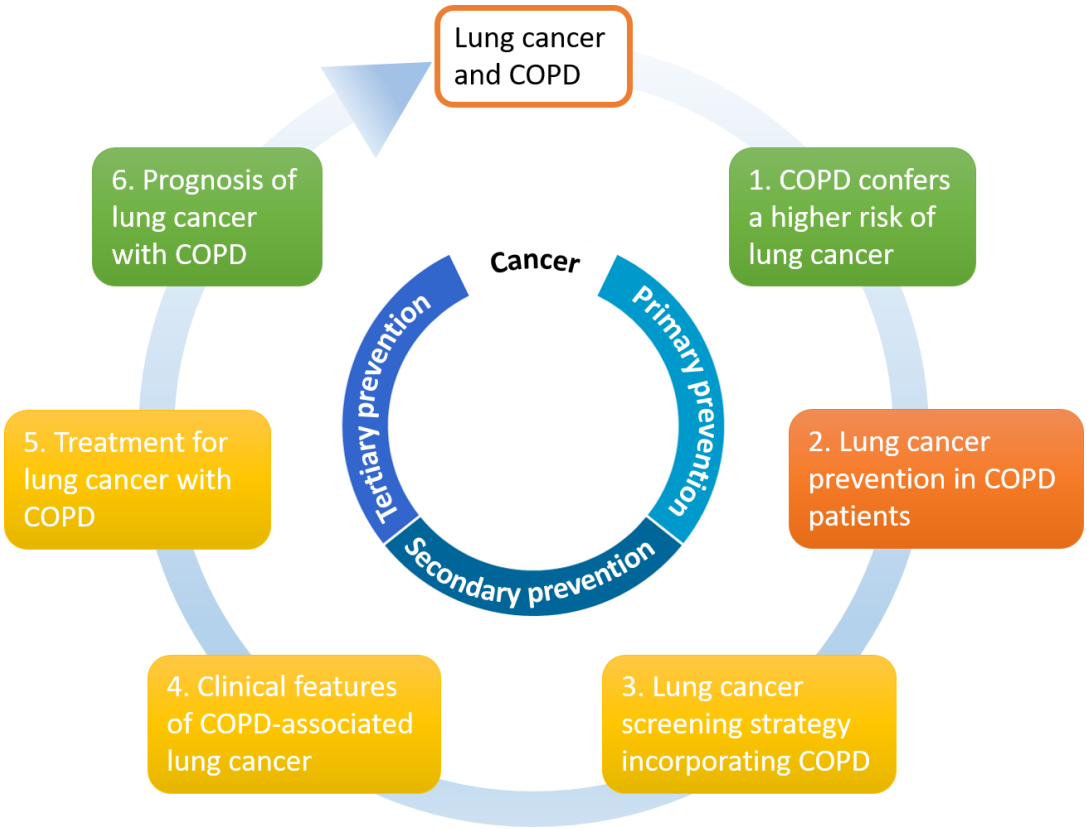


Figure 2.1: Clinical epidemiologic association between COPD and lung cancer in six areas. The color codes refer to the current evidence showing the magnitude of association, where green indicates the association is clearly defined, amber is a debatable issue, and red is poorly understood. COPD: chronic obstructive pulmonary disease.

(i) *Different study populations*. Patient demographic characteristics might have a residual effect on the risk of lung cancer even after adjustment. Several studies revealed that the magnitude of COPD lung cancer association was influenced by

smoking habit[298,301,305]. A large cohort study showed that the odds ratio (OR) for lung cancer prevalence in never smokers with emphysema was six-fold greater than those without emphysema, while the corresponding OR was only two-fold in smokers[301]. In addition, the relationship was modified by sex, with near two-fold amplified risk in women[299,310]. Furthermore, patient previous respiratory disease other than COPD (e.g., pneumonia) could alter the risk of lung cancer[64]; these factors have not been commonly considered in previous analysis on the association between COPD and lung cancer.

(ii) *Distinct methods to determine emphysema*. The presence of emphysema can be detected automatically (densitometry) or visually (direct interpretation by radiologist). Automated analysis can provide reproducible and blinded assessments across studies, and can virtually eliminate subjectivity in the estimation of emphysema[303,311]. In contrast, visual assessment provides the capability of accurately detecting clinically meaningful emphysema and avoiding incorrect interpretation by computer software[312,313]. In the context of lung cancer risk, a recent meta-analysis revealed that the COPD lung cancer association was only significant for visually determined emphysema[314].

(iii) *Variable definitions of airflow obstruction*. A ratio of FEV_1 and FVC of less than 0.7 was generally used to define airflow obstruction[304]; however, other indices, such as FEV_1/FVC under the lower limit of normal criteria, and reduction of FEV_1% predicted, were also considered indicative of airway obstruction and applied in the research[310,315,316]. The use of inconsistent parameters for labelling airflow obstruction may give rise to conflicting results.

Table 2.1: Lung cancer risk according to airflow limitation and emphysema

study	case vs. control	sex, female	smoking status	Evaluation of emphysema, associated lung cancer risk, OR (95%CI)	Measurement of airflow limitation, associated lung cancer risk, OR (95%CI)
Schwartz et al.[307] (2016, n=1093)	341 vs. 752	54.3%	never: 2.8% ever: 97.2%	emphysema on qCT_{-950HU}: 2.66 (1.80, 3.95)¶ emphysema by radiologist read: 1.80 (1.35, 2.41)¶ self-reported emphysema: 1.87 (1.25, 2.79)¶	spirometry $FEV_1/FVC<0.7$: 1.98 (1.50, 2.61)¶ self-reported COPD: 1.43 (1.05, 1.94)¶
Wang et al.[308] (2012, n=2201)	1069 vs. 1132	31.7%	never: 47.7% ever: 52.3%	self-reported emphysema: 1.92 (1.31, 2.81)§ self-reported emphysema: 1.55 (1.03, 2.32)¶	spirometry $FEV_1/FVC<0.7$: 1.54 (1.21, 1.96)§ spirometry $FEV_1/FVC<0.7$: 1.29 (1.00, 1.68)¶
Maldanado et al.[303] (2010, n=441)	64 vs. 377	61.6%	current: 58.0% former: 42.0%	percent emphysema volume on qCT_{-900HU}: 1.04 (0.82, 1.33)¶	spirometry FEV_1/FVC continuous: 1.29 (1.02, 1.62)¶ spirometry $FEV_1\%$ continuous: 1.15 (1.00, 1.32)¶
Schwartz et al.[299] (2009, n=1126)	562 vs. 564	100%	never: 49.2% smoker: 50.8%	self-reported emphysema: 3.21 (1.60, 6.45)¶	self-reported COPD#: 1.67 (1.15, 2.41)¶
Koshiol et al.[298] (2009, n=4042)	1934 vs. 2108	22.4%	never: 20.1% former: 43.0% current: 36.9%	self-reported emphysema: 3.8 (2.8, 5.1)¶ self-reported emphysema: 1.9 (1.4, 2.7)‡	self-reported COPD#: 4.1 (3.4, 4.9)¶ self-reported COPD#: 2.5 (2.0, 3.1)‡
Wilson et al.[300] (2008, n=3638)	99 vs. 3539	48.6%	current: 60.2% ex-smoker: 39.8%	emphysema by radiologist read: 4.39 (2.76, 6.99)§ emphysema by radiologist read: 3.56 (2.21, 5.73)¶ emphysema by radiologist read: 3.14 (1.91, 5.15)‡	spirometry $FEV_1/FVC<0.7$: 2.89 (1.89, 4.43)§ spirometry $FEV_1/FVC<0.7$: 2.09 (1.33, 3.27)¶ spirometry $FEV_1/FVC<0.7$: 1.41 (0.87, 2.29)‡

Table 2.1: Lung cancer risk according to airflow limitation and emphysema

study	case vs. control	sex, female	smoking status	Evaluation of emphysema, associated lung cancer risk, OR (95%CI)	Measurement of airflow limitation, associated lung cancer risk, OR (95%CI)
de Torres et al.[304] (2007, n=1166)	23 vs. 1143	26%	former: 100%	emphysema by radiologist read: 3.33 (1.41, 7.85)[§] emphysema by radiologist read: 3.13 (1.32, 7.44)[¶] emphysema by radiologist read: 2.51 (1.01, 6.23)[‡]	spirometry $FEV_1/FVC<0.7$: 4.83 (2.05, 11.41)[§] spirometry $FEV_1/FVC<0.7$: 2.89 (1.14, 7.27)[¶] spirometry $FEV_1/FVC<0.7$: 2.10 (0.79, 5.58)[‡]
Kishi et al.[309] (2002, n=120)	24 vs. 96	58.3%	former: 45% current: 55%	percent emphysema volume on qCT_{-900HU}: 1.1 (0.6, 1.9)[¶]	spirometry FEV_1/FVC continuous: 1.4 (1.0, 2.2)[¶] spirometry FEV_1% continuous: 1.2 (1.0, 1.5)[¶]

OR: odds ratio; CI: confidence interval; FEV_1: post-bronchodilator forced expiratory volume in 1 second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

[§]unadjusted analysis; [¶]adjusted for patient demographics; [‡]adjusted for patient demographics, and emphysema or airflow limitation, as appropriate.

[#] including reports of emphysema, COPD, and/or chronic bronchitis.

Apart from the three aforementioned factors, timing of COPD diagnosis[298,305], degree of airflow obstruction[246,303] and severity of emphysema[300,312] have also been reported to exert a remarkable effect on the significance and/or the magnitude of the impact of COPD on lung cancer risk. Although no solid evidence is available at present to clearly distinguish roles of airflow obstruction and emphysema in lung cancer development, it is certain that the highest lung cancer risk occurs when airflow obstruction and emphysema coexist[304,307]. A prospective cohort from the lung cancer screening study demonstrated two- and eleven-times higher incidence density of lung cancer among individuals with both diseases as compared to those with either one of them and those with neither one[304]. Therefore, both airflow obstruction and emphysema should be regarded as risk factors for lung cancer, and as such, could help identify individuals who may need active interventions to preempt tumorigenesis and target population who may benefit most from cancer screening.

2.1.2 Lung cancer prevention in COPD

2.1.2.1 Minimizing tobacco exposure

Since lung cancer is one of the most common causes of death among COPD patients[317], the task to preempt lung cancer in COPD is critical. Cigarette smoking is the main element that these two diseases share in common, and it conferred an additional lung cancer risk in patients with preexisting COPD[318]. So the first priority of lung cancer preventive measures is smoking cessation. A population-based cohort study with 31-year follow-up demonstrated that participants who quit smoking reduced their lung cancer risk by 50%[46]. The Lung Health Study, which enrolled 5,887 smokers with asymptomatic airflow obstruction (FEV_1/FVC ≤70%), further confirmed that lung cancer mortality could be improved most by smoking cessation[319], with rates of 6.04 per 1,000 person-year in those who quit smoking and 11.09 per 1,000 person-year in continuing smokers ($p<0.001$).

Secondhand tobacco smoke (SHS) exposure is another important risk factor for lung cancer[49]. Henschke and colleagues revealed that emphysema increased the risk of lung cancer in never smokers while the SHS exposure was an independent indicator of emphysema[301]. In addition, Kim and colleagues pooled data from 18 case-control studies in the International Lung Cancer Consortium (ILCCO)[49], and found that SHS exposure was associated with an increased risk of lung cancer among both ever smokers and never smokers, and that risk of lung cancer increased with increasing years of SHS exposure. Therefore, SHS exposure should be avoided in COPD patients at the same time.

2.1.2.2 Pharmacologic chemoprevention

Inhaled corticosteroids (ICS), which are commonly prescribed to COPD patients,

are now showing a potential cancer prevention effect[320]. A nested case-control study of patients with COPD demonstrated that regular use of ICS was significantly associated with a decreased lung cancer risk[321]. Moreover, Parimon and colleagues observed a dose-response relationship where higher doses of ICS (≥1,200 ug/d) conferred a risk reduction of lung cancer of 61% in COPD patients[322].

Statins could attenuate the inflammation in COPD[323,324] and have potential anticancer effects[325,326]; however, two recent meta-analyses indicated no significant association between statin use and the risk of lung cancer[327,328]. For patients with COPD who are already at an increased risk of developing lung cancer, Liu and colleagues found that COPD patients who used statins exhibited a 63% reduced lung cancer risk[329]. Although the data on chemopreventive agents (i.e., ICS and statin) at present are not as definitive as smoking cessation, it is axiomatic that the above-mentioned measures could help not only reduce the incidence of lung cancer but also mitigate the progression of COPD.

2.1.3 Lung cancer screening in COPD

Low-dose CT (LDCT) is recommended for lung cancer screening by the United States Preventive Services Task Force (USPSTF)[330], which contributed to earlier detection of lung cancer and a significant reduction in mortality[331,332]. However, a recent report showed an increasing number of patients with newly diagnosed lung cancer falling outside the population suggested by USPSTF eligibility criteria for screening[47], implicating the need for a more sensitive screening strategy. Since patients with COPD, regardless of airflow obstruction or emphysema, are at higher risk for developing lung cancer[296,302], several studies have targeted this population as a candidate for lung cancer screening[302,315,333]. Lowry and colleagues compared the health benefits of different screening programs, and the results showed that a

program using lower pack-year thresholds (≥1 pack-year) for individuals with COPD could yield higher life expectancy gains than USPSTF using smoking history alone[315]. Meanwhile, the detection rate and diagnostic precision could be improved by adding CT-detected emphysema as a complementary entry criterion to the National Lung Screening Trial (NLST)[302]. With respect to survival advantage, results from the Danish Lung Cancer Screening Trial indicated a favorable effect of screening on lung cancer mortality in COPD patients[334]. In order to increase the implementation of lung cancer screening among COPD patients, however, several aspects should be considered.

2.1.3.1 Underdiagnosis and overdiagnosis of COPD

It has been demonstrated that COPD is remarkably under-diagnosed worldwide, with an estimated rate of underdiagnosis of 71.2%-81.4%[155,156]. Overdiagnosis of COPD also poses a clinical challenge; 30.4%-40% of patients with a prior COPD diagnosis were found to have normal lung function on spirometry[335,336]. As a result, recommendation for lung cancer screening in self-reported COPD would only benefit a limited population, leaving four-fifths of cases unrecognized and one-third over-treated. Evidence on airflow obstruction and/or emphysema are therefore the ideal surrogates in the context of lung cancer screening. Young and colleagues[337] argued for a widespread use of spirometry screening for airflow obstruction in asymptomatic smokers, in an attempt to appropriately evaluate the prevalence of COPD and detect individuals at an increased risk for lung cancer early. Some identified determinants of under-diagnosed COPD include male sex, lower level of education, being of ethnic minority, and lower comorbidity burden[155,156,160], while younger age, being overweight, and higher levels of comorbidities are risk factors for COPD overdiagnosis[160,164,338]. Therefore, individuals with these characteristics should be offered spirometry for a correct diagnosis of COPD, which in turn will allow for further risk stratification in lung

cancer screening[339]. Since the presence of emphysema is primarily diagnosed by CT and most individuals do not have a CT scan beforehand, the value of emphysema in selecting candidates for the baseline lung cancer screening is thus limited. However, the identification of emphysema during baseline screening would be conducive to determining individuals who may need close follow-up[304].

2.1.3.2 Further risk assessment

As COPD is identified as a driving factor in lung cancer, a refined risk stratification among patients with preexisting COPD can further improve the cost-effectiveness of CT screening and avoid unnecessary radiation exposure[340]. De-Torres and colleagues explored risk factors associated with lung cancer development in a cohort of outpatients with COPD, and identified four independent predictors: baseline age, body mass index (BMI), predicted percentage of diffusion capacity for carbon monoxide (DLCO%), and GOLD stages[246].

Subsequently, the COPD-specific score (COPD-LUCSS) was developed to predict lung cancer risk for patients with COPD[318]. COPD-LUCSS is determined by four parameters: age >60, BMI <25kg/m^2, pack-years >60, and presence of radiological emphysema, with a total range from 0 to 10 points (Table 2.2). In comparison to those with low-risk (scores 0-6), patients in high-risk category (scores 7-10) had a 3.5-fold greater risk of developing lung cancer. As COPD could be a driving factor in lung cancer, these results further indicated a risk stratification among COPD patients. Therefore, screening strategy based on COPD-LUCSS system allows for further reduction in cost and screening-related harms.

Table 2.2: COPD-LUCSS and COPD-LUCSS-DLCO scoring system

COPD-LUCSS[a]		COPD-LUCSS-DLCO[b]	
components	Score	components	Score
body mass index <25	1	body mass index <25	1.5
pack-year history >60	2	pack-year history >60	1
age >60 year	3	age >60 year	2.5
radiologic emphysema	4	DLCO <60%	3
total	10	total	8
categories		categories	
low risk	0-6	low risk	0-3
high risk	7-10	high risk	3.5-8

[a] predictive score for lung cancer risk for patients with COPD; [b] identification of COPD patients at high risk of lung cancer mortality. COPD: chronic obstructive pulmonary disease; DLCO: diffusion capacity of lung for carbon monoxide

2.1.3.3 Over-diagnosis of pulmonary nodules

Over-diagnosis refers to excess lung cancer detected by screening that would not affect the patient during their lifetime if left untreated[341], which may incur additional cost, patient anxiety, and potential morbidities related to subsequent diagnostic procedures[342]. It is estimated that over-diagnosis accounted for as much as 18.5% of all lung cancers detected by LDCT[343]. Seeing that COPD is associated with more aggressive forms of lung cancer[344,345], over-diagnosis in this high-risk population may be less likely. De-Torres and colleagues found that screening in COPD patients resulted in a higher detection rate of early-stage lung cancer, without showing a significant "histology shift" towards over-diagnosis[333,346]. Young and colleagues examined the effect of COPD on over-diagnosis and demonstrated that LDCT screening in COPD patients yielded a doubling of lung cancer incidence without apparent over-diagnosis, whereas in non-COPD patients, the stage shift was counterbalanced by the excess diagnosis of bronchioloalveolar carcinoma[347]. The available data suggest that lung cancer screening in individuals with COPD may contribute to a high rate of diagnosis

of lung cancer at curable stage while minimizing over-diagnosis[347,348].

2.1.3.4 Competing causes of mortality/morbidity

The USPSTF recommended that screening should not be offered to people who have substantial comorbid conditions with limited life expectancy[330]. Sin and colleagues reviewed the underlying causes of death in COPD patients and reported that the main cause of death for mild-to-moderate COPD was lung cancer, while for more advanced COPD, respiratory failure was the predominant cause[317]. As regards benefit from screening, De-Torres and colleagues explored the impact of screening on lung cancer mortality in patients with mild-to-moderate COPD[333], and the results showed that the mortality incidence densities from lung cancer were significantly lower in the screening group (0.08/100 person-years) than in the control group (unscreened COPD, 2.48/100 person-years), justifying active screening in patients with milder COPD. However, screening patients with more severe COPD may reduce cost-effectiveness because the benefits could be surpassed by other competing causes of death inherent to COPD[175]. In preliminary data from a post-hoc analysis of the NLST, it has been shown that the lung cancer specific mortality reduction in screening participants with COPD was approximately one half that of those without COPD (15% vs 28% respectively), suggesting the benefits of CT screening in COPD may be diluted by competing causes of death[349,350]. Therefore, the trade-off between the potential benefits and harms should be considered by participants and their health providers together, when considering lung cancer screening in patients with more severe COPD[340].

2.1.4 Clinical features of COPD-associated lung cancer

It has been demonstrated that squamous cell carcinoma is more commonly seen in the setting of COPD[246]. Research on emphysema also indicated its association with squamous cell type (OR, 2.6; 95%CI, 1.4-4.8), even after adjustment for COPD diagnosis and smoking history[351]. A shared predisposing factor -tobacco smoking- may account for this observation[344].

Lung cancer arising in COPD was more likely to be centrally located[352]. Similarly, emphysema severity was indicative of tumor location in COPD-associated lung cancer, as lower emphysema grade had a tendency towards central location of lung cancer while higher grade towards peripheral location[352]. When the extent of emphysema was quantified regionally, a strong association was found for cancer being located in the area with the highest degree of emphysema, with a corresponding OR of 1.342 (95%CI, 1.112-1.620)[353]. Apart from the cancer site, the emphysema severity of the region where tumor occurred was correlated to tumor size[354].

In histopathologic analysis, Schiavon and colleagues described that COPD-associated adenocarcinoma tended to manifest less invasive characteristics, such as increased lepidic component and lower cell proliferation, as compared to COPD-free adenocarcinoma[355]. However, Murakami and colleagues commented that cancer arising in emphysematous lung possessed a more aggressive nature[356], because the matrix metalloproteinase (MMP), which was widely up-regulated in emphysematous lungs, was associated with the occurrence of lymphovascular invasion and postoperative recurrence[345,356]. Moreover, in post-hoc analyses of two CT screening studies, it has been shown that smokers with impaired lung function had shorter volume doubling times of pulmonary nodules (more aggressiveness) and less prevalence of indolent lung cancers, suggesting COPD is a clinical marker of aggressive lung cancer[357-359].

With regard to molecular features, several studies found that both EGFR mutations and ALK rearrangements were less prevalent in COPD-associated lung cancer[360,361], and the presence of EGFR mutations was inversely correlated with the severity of airflow limitation[361]. In contrast, KRAS mutations were independent of COPD status[362,363]. It is worth mentioning, however, that the traits of driver genes alternations in lung cancer with COPD could be partly due to their associations with patient clinical characteristics[362].

2.1.5 Treatment for lung cancer coexisting with COPD

Major lung resection is the best option for cure in lung cancer patients; however, it has been reported that about one-third of patients with comorbid COPD may be ineligible for surgery for lung cancer that would otherwise be technically operable, due to poor physical condition[360]. Furthermore, the frequencies of all postoperative pulmonary complications (PPCs), including pneumonia (10.1%-16.2% in COPD patients following lung cancer surgery)[364-366], atelectasis (3.5%-15.4%)[365,367], empyema (2.2%-8.3%)[366], and persistent air leak (12%-16.2%)[364,368], and prolonged mechanical ventilation (4%-16.7%)[366-368] were often higher in COPD patients[369]. Therefore, an accurate risk assessment in patients with lung cancer coexisting with COPD is critically important, in order to optimize treatment for these patients.

2.1.5.1 Identifying risk factors for PPCs

There are only a small number of studies to date that have investigated risk factors for PPCs in COPD patients undergoing lung cancer surgery. Kim and colleagues, in their prospective study, reported that the incidence of PPCs was higher in patients with COPD but not different between COPD grades (FEV_1% ≥70% vs. FEV_1% <70%) or

symptom burden (less symptoms vs. more symptoms)[365]. Multivariate analysis revealed that BMI (OR=0.8), DLCO% (OR=0.97), and operation time (OR=1.01) were significant predictors of PPCs in COPD patients undergoing cancer surgery. In cardiopulmonary exercise testing, peak oxygen uptake (VO_{2peak}) is an important parameter in the assessment of surgical risk[370]. Rodrigues and colleagues found that the cutoff value of 61% for VO_{2peak}% (ml/kg/min) was a significant discriminator between COPD patients with and without complications following tumor resection[371]. With regard to surgical approach, Jeon and colleagues performed a propensity score-matched analysis and demonstrated that video-assisted thoracoscopic surgery in lung cancer patients with comorbid COPD could reduce PPCs compared with thoracotomy[372]. Thus, such identified risk factors are supposedly taken into consideration in preoperative risk assessment.

2.1.5.2 Effective perioperative management

Patient functional status must be optimized during the preoperative workup. Medical management for COPD, smoking abstinence, and pulmonary rehabilitation are three major effective strategies to improve postoperative outcomes[370,373]. Pharmacologic therapy for COPD, such as bronchodilators and ICS, can help reduce symptoms, prevent exacerbations, and thus increase perioperative safety[365,374]. The use of ICS was thought to pose an increased risk of pneumonia[375], but a recent study has demonstrated no relationship between the perioperative ICS administration and the incidences of PPCs in COPD patients receiving pulmonary resection for lung cancer, justifying the use of ICS during the perioperative period[376].

It is clear that smoking cessation should be advocated preoperatively which helps to not only reduce PPCs but improve quality of life (QOL) and long-term survival[370,377]. However, the timing of tobacco cessation is still controversial. Although a general trend

was observed for decreasing PPCs with an increase in the length of cessation prior to surgery[378], some studies, were not as supportive, showing a higher risk for PPCs in patients who had quit smoking in the immediate preoperative period[379,380]. Hypothetical explanations for this increased risk may relate to the effect of nicotine withdrawal and increased sputum volume caused by the reduction in irritant-induced coughing, before the recovery of ciliary function[381]. Therefore, smoking cessation should be encouraged with sufficient duration (2-4 weeks) before surgery[373].

Pulmonary rehabilitation programs are widely applied in the nonpharmacologic management of moderate-to-severe COPD, which yields an improvement in exercise capacity[134]. The effect of preoperative pulmonary rehabilitation has now been demonstrated in patients with COPD undergoing lung cancer resection[382-384]. Stefanelli and colleagues randomly divided 40 patients with concomitant lung cancer and COPD into two groups[382]; VO_{2peak} displayed a remarkable improvement in the group receiving 3-week intensive pulmonary rehabilitation (from 14.9±2.4 to 17.8±2.1 ml/kg/min, $p<0.001$), while no change was found in the control group. Similarly, Divisi and colleagues targeted 27 patients with compromised lung function and observed a significant increase in FEV_1 (from mean FEV_1 of 1.14L to 1.65L) after a 4-week preoperative pulmonary rehabilitation[385]. Moreover, pulmonary rehabilitation is shown to decrease postoperative complications as well as length of hospital stay[384]. Despite the small sample size included in previous studies[384-386], the documented benefits underscore the importance of pulmonary rehabilitation for patients with advanced COPD prior to lung cancer surgery, to help to reduce the function limitations of inoperability.

2.1.5.3 Predictors of lung volume reduction effect

Patients with lung cancer and COPD receiving cancer resection may have a

minimal loss, or improvement, in postoperative pulmonary function, which is referred to as the "lung volume reduction effect"[387,388]. Various methods have been reported to determine potential candidates who are more likely to have the functional benefit. Korst and colleagues defined the COPD index, a scoring system combining preoperative FEV_1% predicted and FEV_1/FVC[389], and found that COPD index <1.0 was a good indicator of an improvement of pulmonary function following lobectomy. Sekine and colleagues documented a greater actual postoperative FEV_1 than predicted in COPD patients with lobectomy of lower portion[390]. Furthermore, quantitative analysis of radiologic emphysema could characterize the respiratory dynamics underlying the volume reduction effect[391]. Alternatively, a concomitant surgery of tumor resection and lung volume reduction surgery (LVRS) is feasible in patients who satisfy the criteria for both LVRS and cancer surgery[392]. This combination offers the best opportunity to cure lung cancer, treat COPD/emphysema, and thus yield a survival advantage during one surgical procedure[393]. The intraoperative strategies, such as lobectomy combined with contralateral LVRS, are highly dependent on the site of tumor, heterogeneous distribution of emphysema, patient's attitude, as well as surgeon's experience.

2.1.5.4 Non-surgical treatment

Patients who are unfit for surgery due to poor lung function and/or COPD-related systemic comorbidities (such as ischemic cardiac disease) could benefit from stereotactic body radiotherapy (SBRT), which has been shown as a safe and effective alternative treatment for early-stage lung cancer[394]. A recent study by Pamla and colleagues reported a 3-year actual local control rate of 89% in stage I non-small cell lung cancer (NSCLC) patients with concomitant COPD (GOLD class III/IV) after SBRT[395], and a subsequent systematic review demonstrated comparable outcomes between

SBRT and surgery in this patient population[395]. The toxicity following SBRT was tolerable, and even milder in patients with COPD than those with normal lung function[396]. Data on the effectiveness of chemotherapy in COPD-associated lung cancer remain limited, although COPD has been reported to increase the risk of chemotherapy-induced febrile neutropenia[397].

2.1.5.5 Multidisciplinary treatment (MDT)

MDT can improve adherence to evidence-based guidelines and timeliness of care for lung cancer patients[398]. In addition, in the setting of advanced NSCLC, MDT has been reportedly associated with a better survival rate[399]. Since lung cancer and COPD often coexist, pulmonologists could provide prompt diagnosis for lung cancer and effective management of pulmonary comorbidities[400]. Data from the Surveillance, Epidemiology and End Results (SEER) database showed that the involvement of pulmonologists in the care of patients with early-stage NSCLC and COPD could increase surgical resection rate (OR, 1.26; 95%CI, 1.11-1.45) and reduce mortality risk (HR, 0.80; 95%CI, 0.75-0.85)[401]. Thus, MDT should be incorporated into the treatment of lung cancer concomitant with COPD.

2.1.6 Role of COPD in lung cancer prognosis

The prognostic significance of COPD in lung cancer remains equivocal. Most studies found that COPD exerted an unfavorable effect on lung cancer prognosis[366,402,403], while others did not[404,405]. Two recent meta-analyses indicated COPD as an adverse prognostic predictor, but the results suffered from a high level of heterogeneity between studies[406,407]. The heterogeneity of effect size is possibly subject to cancer stage, treatment modality and status of COPD *per se*[407]. Zhai and

colleagues found that coexisting COPD was associated with worse survival (HR, 1.41; 95%CI, 1.13-1.75) in patients with early-stage NSCLC undergoing surgical resection[402]. However, this association was insignificant (HR, 1.20; 95%CI, 0.83-1.50) in the study by Izquierdo and colleagues[404], who targeted patients with advanced lung cancer (stage IIIB/IV) treated with chemotherapy. In terms of COPD grade, there was a more apparent decrease in survival for patients with severe COPD, but not for those with mild-to-moderate COPD, as compared to non-COPD patients following lung cancer resection[366,408]. In addition, quantitative analysis of emphysema on CT demonstrated a direct association with lung cancer mortality (HR, 1.21; 95%CI, 1.06-1.38)[313].

Recently, a prognostic model was designed to identify patients with COPD at high risk of lung cancer death[409]. In this model (COPD-LUCSS-DLCO), a corresponding score was assigned to each indicator: patient's age (2.5 points), BMI (1.5 points), pack-year of smoking (1 point), and DCLO% (3 points); participants were then classified into low risk (scores 0-3) and high risk group (scores 3.5-8), where the latter conferred a 2.4-fold (95%CI, 2.0-2.7) increased risk of death when compared to the low-risk category (Table 2.2)[409]. In addition, research from the linked SEER-Medicare Database demonstrated the addition of comorbid COPD to a comprehensive model could improve prognostication over similar models using cancer information alone[410].

With regard to health-related quality of life, Pompili and colleagues performed a propensity score-matched analysis among patients undergoing lobectomy for lung cancer, and found that patients with COPD experienced a comparable postoperative quality of life to matched patients without COPD[411]. Pompeo and colleagues studied patients who underwent tailored combined surgery for both stage I NSCLC and severe emphysema, and demonstrated a significant improvement in general health domain based on short-form 36 item questionnaire after surgery, associated with improvements in dyspnea index and exercise capacity[412].

2.1.7 Cancer prevention strategy and future efforts

Lung cancer prevention strategies should be emphasized and encouraged throughout the entire disease process. Primary prevention is aimed at limiting the incidence of lung cancer. COPD, characterized as either airflow obstruction or emphysema, is an important predisposing factor for lung cancer development. Thus, a primary aim is to control the additional exposures (such as smoking and SHS exposure) which contribute to COPD, lung cancer, and the progression from COPD to lung cancer. The use of chemopreventive agents such as ICS and statin remain relatively rudimentary in COPD patients, and should be tested in prospective, controlled trials. Secondary prevention refers to the early detection of lung cancer at a pre-clinical phase, and lung cancer screening represents the most important component of this approach. The current available evidence shows that lung cancer screening in COPD patients confers a high detection rate of cancer at early stage (stage shift), and reduces lung cancer mortality. Nevertheless, some screening-related issues (e.g., underdiagnosis of COPD and potential benefit offset) ought to be recognized and discussed in the future. With respect to clinical features, lung cancer in COPD is quite distinct from that in non-COPD, highlighting the demand for a designated screening criteria as well as a tailored treatment algorithm in this patient population. Tertiary prevention points to the execution of treatment and rehabilitation with the principal aim of alleviating disability and improving the outcomes of illness. Surgery for lung cancer in COPD may have a lung volume reduction effect. Precise risk assessment, optimal preoperative management (smoking cessation, medical treatment for COPD, and pulmonary rehabilitation), and MDT care are critically important before surgery. Meanwhile, the recognition of the effect of COPD on lung cancer prognosis enables refined prognostication and thus allows for personalised clinical decision-making. Increasing understanding of the relationship between COPD and lung cancer will allow the development of better cancer preventive strategies and ultimately will improve

the outcomes of this patient population.

2.2 Genetic Association between Lung Cancer and COPD

As already discussed in section 2.1, COPD and lung cancer are inextricably linked in many clinical aspects; however, the exact mechanisms connecting COPD and lung cancer remain obscure. Tobacco exposure is a common risk factor for both lung cancer and COPD, but these two diseases have been demonstrated to be linked by more than smoking alone; only 15-20% of smokers develop lung cancer and/or clinically significant COPD, while 10-15% of individuals with either of these disease turn out to be never smokers[299,413]. Therefore, additional intrinsic factors might be responsible for the association between COPD and lung cancer.

Several hypotheses are being proposed, such as chronic inflammation and associated pro-inflammatory mediators, oxidative and noxious stress, and epithelial to mesenchymal transition (Figure 2.2)[167,414,415].

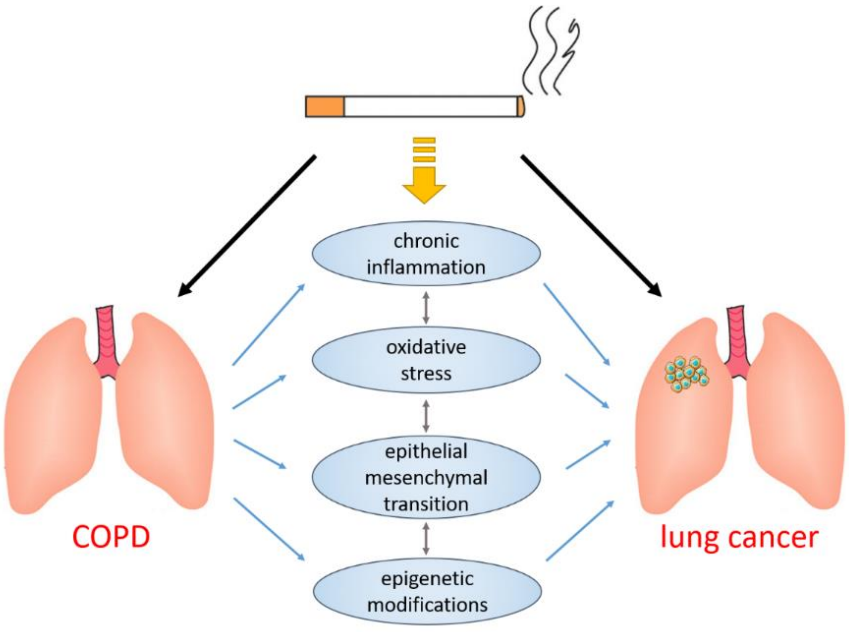


Figure 2.2: Putative mechanisms linking chronic obstructive pulmonary disease and lung cancer.

Generally, pulmonary chronic inflammation resulting from smoking and COPD plays a central role in the development of lung cancer, which results in repeated epithelial cell injury and high cell turnover, subsequently leading to accumulation of DNA replication errors and initiation of carcinogenesis (Figure 2.3)[416]. Meanwhile, several pro-inflammatory cytokines (e.g., IL-1β, IL-6), and, in particular, activation of nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) have also been implicated in the progression from COPD to lung cancer by means of inhibiting apoptosis, inducing proliferation, and, finally, accelerating cancer development[417,418].

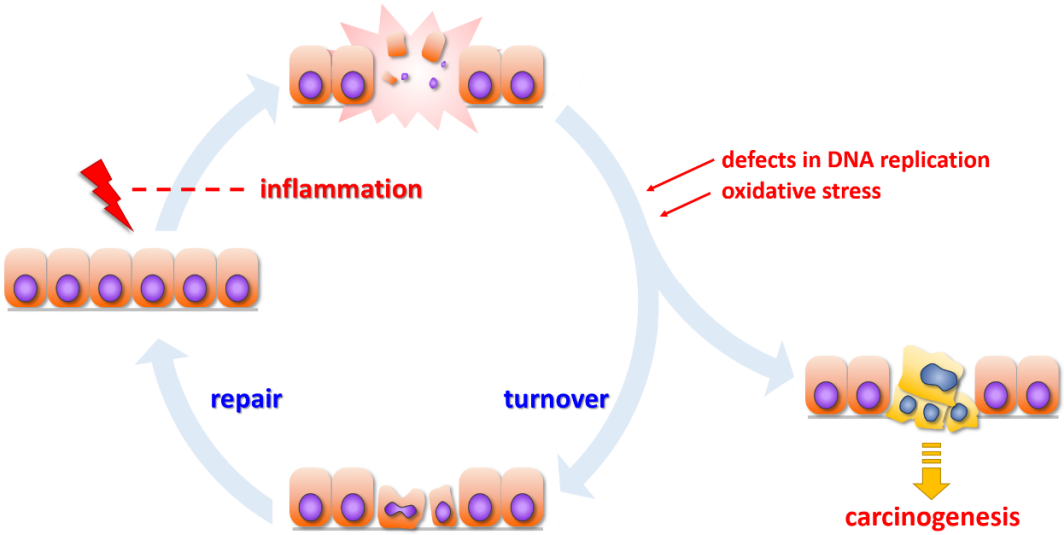


Figure 2.3: Repetitive cycles of cell injury and turnover in the context of chronic inflammation.

Additionally, oxidative stress is considered as a causative agent of both diseases[344]; an imbalance between oxidants and antioxidants can drive free radical damage of DNA (point mutations, single and/or double stand breaks, and DNA cross-linking), which if incorrectly repaired, contributes to the earliest stage of tumorigenesis[344].

Epithelial-mesenchymal transition (EMT) represents a process whereby cells with an epithelial phenotype transform into cells with a mesenchymal phenotype, in which transformed cells are endowed with the ability to invade, resist apoptosis and disseminate[415]. The process is commonly promoted by transforming growth factor-β

(TGF-β) and matrix metalloproteinase (MMP) that underlie COPD, contributing to malignant transformation of the respiratory epithelium (Figure 2.4)[419].

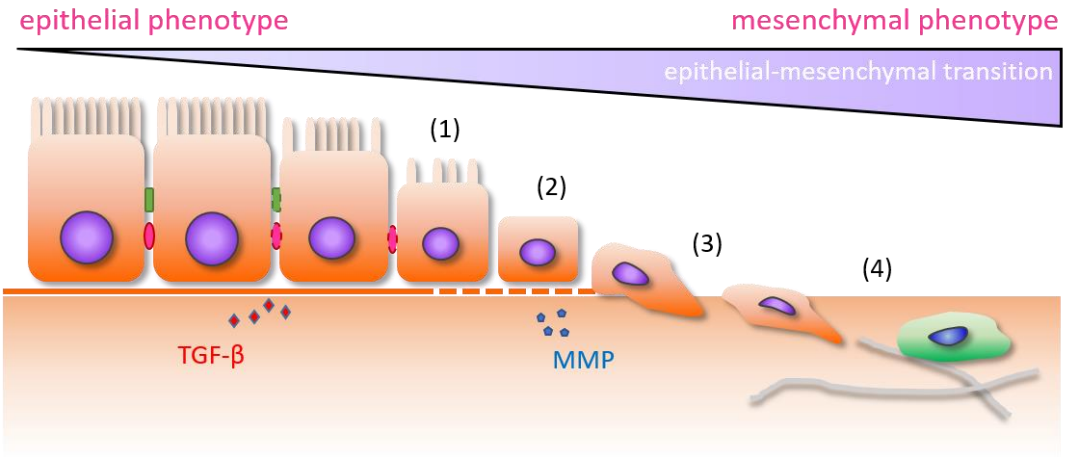


Figure 2.4: Process of epithelial-mesenchymal transition (EMT). (1) tight-junction dissociation and loss of microvilli; (2) loss of cell polarity; (3) cytoskeleton reorganization and migration; (4) invasion.

Collectively, chronic inflammation in COPD may increase the probability of aberrant mutations in airway and/or alveolar epithelium that promotes tumor initiation and progression. Meanwhile, the abnormal inflammatory response alongside pro-inflammation mediators may lead to excessive oxidative stress, which in return activates proliferative and inflammatory pathways and favors carcinogenesis through DNA damages[420]. In these circumstances, bronchial epithelial cell integrity and function are disrupted by matrix remodeling and growth factor release (TGF-β and MMP), and together trigger EMT[421], accelerating tumor growth and angiogenesis.

In addition, epigenetic modifications play a part in the mechanistic links[422]. Tobacco smoking induces a myriad of DNA methylation (for example genes such as CCDC37, MAP1B)[423] and histone acetylation (HDAC2)[344], as well as changes in microRNA expression (let-7c)[424]. Some of these patterns have been demonstrated to predispose an individual to both COPD and cancer. Importantly, from a clinical standpoint, the reversible nature of epigenetic modulations provides a promising chemopreventive target for lung cancer and COPD together.

Although the basis of the link between COPD and lung cancer has not been clearly elucidated at the biological level, genetic association studies are now attempting to clarify this important relationship. Genetic association analysis is based on a case-control study to compare the difference in allele frequencies between groups of affected and unaffected individuals at the population level[425], aiming to detect association between one or more genetic polymorphisms and disease risk[426]. Historically, it includes two major types of investigation to determine the contribution of genes to disease susceptibility: the genome-wide association approach and the candidate gene approach.

2.2.1 Genome-wide association studies on COPD and lung cancer

The term genome-wide association (GWA) study refers to a case-control association study using high-throughput genotyping techniques to assess hundreds of thousands of single nucleotide polymorphisms (SNPs) that span the whole genome, and to relate them to clinical conditions and measurable traits (Figure 2.5)[427]. The GWA study design is based on the common disease common variant hypothesis, and, rare variants are poorly captured by GWA approach[428].

So far, published GWA studies for COPD and lung cancer have identified several risk loci, and some of them overlap (Table 2.3). One of the loci, which specifically modulates susceptibility to both diseases, is located on chromosome 15q25 and maps to the *CHRNA3* and *CHRNA5* (cholinergic receptor, nicotinic, subunits α3 and α5) genes which encode neuronal nicotinic acetylcholine receptors (nAChR)[429-431].

Table 2.3: Chromosomal loci and candidate/nearest genes associated with COPD and lung cancer identified by genome-wide association studies.

region	candidate or nearest gene	region	candidate or nearest gene
COPD		lung cancer	
1q23	RPL31P11[432]	3q28	TP63[433-435]
1q41	TGFB2[436]	3q29	XXYLT1[437]
4q22	FAM13A[438]	5p15	TERT[433,434,439,440], CLPTM1L[439]
4q31	HHIP[436,441]	6p21	BAT3[440], HLA class II region[434], FOXP4-AS1[442]
7p15	NUPL2[443]	6q22	ROS1[434]
11q14	DLG2[443]	9p21	CDKN2B-AS1[442,444]
11q22	MMP12[436]	10q25	VTI1A[434]
14q32	RIN3[436]	12q23	SLC17A8[445]
15q25	**CHRNA3/5**[436,441]	13q12	MIPEP[433]
19q13	RAB4B, EGLN2, MIA and CYP2A6[446]	13q13	BRCA2[435]
		13q31	GPC5[447]
		15q25	**CHRNA 3/5**[430,431,440], PSMA4[431], HYKK[430]
		18p11	PIEZO2[448]
		22q12	HORMAD2[433], MTMR3[433], CHEK2[435]

Bold indicates potential overlapped gene implicated in both COPD and lung cancer.

BAT3: HLA-B associated transcript 3; *BRCA2*: breast cancer 2, early onset; *CDKN2B-AS1*: CDKN2B antisense RNA 1; *CHEK2*: checkpoint kinase 2; *CHRNA3/5*: cholinergic receptor, nicotinic, subunits α3 and α5; *DLG2*: discs, large homolog 2 (Drosophila); *FAM13A*: family with sequence familiarity 13 member A; *FOXP4-AS1*: FOXP4 antisense RNA 1; *GPC5*: glypican 5; *HHIP*: Hedgehog interacting protein; *HORMAD2*: HORMA domain containing 2; *HYKK*: hydroxylysine kinase; *MIPEP*: mitochondrial intermediate peptidase; *MMP12*: matrix metallopeptidase 12; *MTMR3*: myotubularin related protein 3; *NUPL2*: nucleoporin like 2; *PIEZO2*: piezo type mechanosensitive ion channel component 2; *PSMA4*: proteasome subunit α4; *RIN3*: Ras and Rab interactor 3; *RPL31P11*: ribosomal protein L31 pseudogene 11; *SLC17A8*: solute carrier family 17 member 8; *TERT*: telomerase reverse transcriptase; *TP63*: tumor protein p63; *TGFB2*: transforming growth factor β2; *VTI1A*: vesicle transport through interaction with t-SNAREs 1A; *XXYLT1*: xyloside xylosyltransferase 1.

Specifically, in GWA analysis, the rs8034191 SNP was significantly associated with lung cancer, with an increased risk for both heterozygous (OR, 1.21; 95%CI, 1.11-1.31)

and homozygous variants (OR, 1.77; 95%CI, 1.58-2.00)[431]. In addition, the minor allele of the same SNP was estimated to have a population attributable risk for COPD of 12.2%[441]. Furthermore, the allelic OR of the *CHRNA3* rs12914385 SNP was 1.29 for the risk of lung cancer (p-value for trend, 4.79×10^{-16})[440] and 1.39 for the risk of COPD (p-value for trend, 2.70×10^{-16})[436].

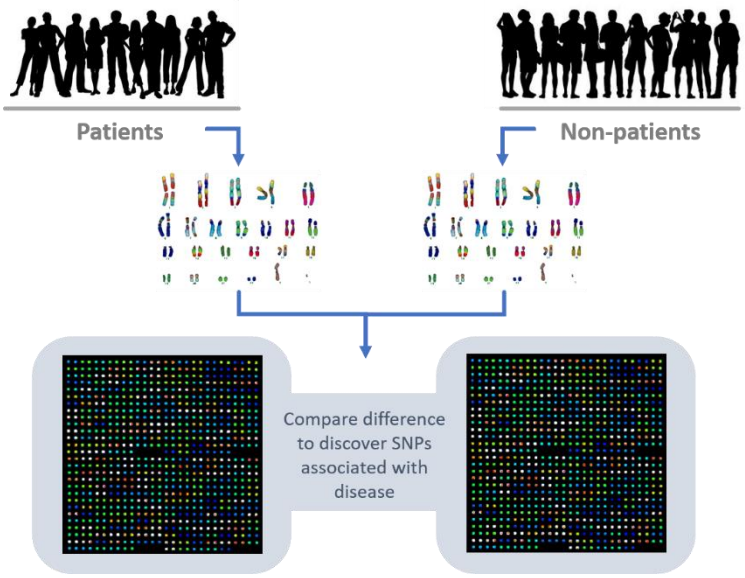


Figure 2.5: Genome-wide association study.

It is also well known that *CHRNA3* and *CHRNA5* are associated with cigarette smoking, and SNP in these genes (e.g., rs16969968 leading to a non-synonymous amino acid change in the α5 subunit) can regulate nicotine dependence[449]. Hence, concerns have been raised about whether this locus has a direct effect on lung cancer and COPD vulnerability, or whether this increased genetic risk of lung cancer and COPD can be explained solely through the genetic influence on nicotine addiction and smoking behaviour[450]. Smoking may serve as the greatest modifiable risk factor in this genetic association. Thorgeirsson and colleagues reported that most of the effect of SNPs in this region might be related to nicotine addition, with only a small direct effect on lung cancer risk[451]. On the contrary, there is also evidence supporting the potential existence of a direct genetic influence of this region on lung cancer and COPD. Several recent GWA studies showed that the genetic association of nicotine receptor SNPs

with lung cancer and COPD remained, after controlling for smoking intensity[436,440]. These observations suggest that lung cancer and COPD may not be discrete diseases, but rather develop through overlapping pathogenetic pathways in individuals who are susceptible to both diseases.

2.2.2 Candidate gene approach as to linking COPD and lung cancer

A candidate gene study focuses on specifically selected genes in which variation is hypothesized to influence the risk of a disease[452]. This is in contrast to GWA studies, which scan the entire genome for common genetic variation influencing disease risk. Normally, candidate genes are selected based on *a priori* knowledge of the gene's biological function[453]. In fact, most genetic associations between COPD and lung cancer have been identified through a candidate gene approach, and a number of candidate genes recognized to relate to both COPD and lung cancer are engaged in pathways involved in the development of both diseases, including inflammation, oxidative stress, and extracellular matrix proteolysis[428]. Hereinafter, emphasis is placed on studies evaluating lung cancer and COPD jointly.

2.2.2.1 *nAChR*

As mentioned above, the SNPs in *nAChR* genes relating to risk of lung cancer and COPD have also been replicated in a number of candidate gene studies[454-456]. Kaur-Knudsen and colleagues examined the associations between the nAChR polymorphism rs1051730, smoking behavior, and tobacco-related diseases in 10,330 participants with 18 years follow-up[454]. Smoking was found to be associated with the development

of lung cancer and COPD, but the smoking behavior-adjusted HRs for homozygotes (TT) versus non-carriers (CC) at rs1051730 were still 1.6 (95% CI, 1.1-2.2) for lung cancer and 1.3 (95% CI, 1.1-1.6) for COPD[454]. Similarly, a recent meta-analysis by Saccone and colleagues[456] reported a significant association of the nonsynonymous *CHRNA5* SNP rs16969968 with lung cancer (OR, 1.31; 95%CI, 1.24-1.38, $p=1.99\times10^{-21}$) and a relatively weak association with COPD (OR, 1.11; 95%CI, 1.02-1.23, p=0.01), after adjusting for number of cigarettes smoked per day. In a Chinese population, Yang and colleagues[455] further analyzed the functional polymorphism of *CHRNA3* in three strata of smoking status (ever smoker, passive smoker, smoking avoider), and observed a significant interaction between ever smoking and rs6495309C genotypes for risk of both diseases (p=0.003 for lung cancer; p=0.048 for COPD). In addition, Wang and Young pointed out that smoking behaviour and COPD had mediating effects on the association between *CHRNA5-A3* region genetic variant and the risk of lung cancer[457,458]. Therefore, in parallel with the GWA studies, the results from candidate gene studies further support a genetic convergence of smoking quantity, lung cancer and COPD susceptibility.

2.2.2.2 *HHIP*

Another locus conferring increased risk of both COPD and lung cancer based on candidate gene studies is 4q31, where the hedgehog-interacting protein (HHIP) is located[415]. *HHIP* is a transmembrane protein which regulates the Hh signaling pathway and manipulates EMT[421]. Thus far, *HHIP* has been demonstrated to correlate with COPD[436,441] and pulmonary function[459,460], and show a week In addition, *HHIP* showed a week association with lung cancer[431]. In the joint analysis of the effect of *HHIP* polymorphisms[461], the GG genotype of the rs1389759 *HHIP* SNP was observed to confer a protective effect on COPD (OR, 0.59; p=0.006) and lung cancer (OR, 0.70;

p=0.05). Moreover, stratification of lung cancer cases into those with and without COPD produced similar results, which could reliably exclude an interactive or confounding effect from coexisting COPD[461,462]. This evidence suggests that not only is COPD a common comorbidity that has possible common origins with lung cancer, but that gene conferring a propensity to COPD may also be significant for lung cancer susceptibility.

2.2.2.3 *TERT-CLPTM1L*

Candidate gene association studies also replicated the variants in the chromosome 5p15 locus in susceptibility to both COPD and lung cancer, which encompasses two potential genes: *TERT* and *CLPTM1L*[462,463]. In contrast to *nAChR*, the *TERT-CLPTM1L* locus was identified to be directly associated with lung cancer, entirely independent of smoking behaviour[439], and this association has been replicated in never smokers[464]. The *TERT* gene encodes human telomerase reverse transcriptase, which is important in the maintenance of telomere length[465], and the *CLPTM1L* (cleft lip and palate transmembrane protein 1-like protein) gene encodes a protein linked to apoptosis in lung cells[425]. Wauters and colleagues[463] studied the rs31489 variant on 5p15 and observed that homozygous carriers of the C-allele exhibited increased susceptibility to bronchial obstruction (OR, 1.82; 95%CI, 1.24-2.69), emphysema (OR, 2.04; 95%CI, 1.41-2.94), and lung cancer (OR, 1.90; 95%CI, 1.21-2.99). Furthermore, when stratifying lung cancer patients into two categories, based on the presence or absence of COPD, rs31489 CC-carriers were almost twice as frequent in patients with COPD as in those without COPD, suggesting the at-risk C-allele is more strongly associated with development of both lung cancer and COPD rather than lung cancer alone[463]. However, this result was not confirmed by Young and colleagues, who reported that *TERT-CLPTM1L* locus predisposed to lung cancer in the absence of

COPD[462].

2.2.2.4 *FAM13A*

Genetic variants in *FAM13A* gene, located at the 4q22 locus, have been associated in a number of GWA studies with lung function[429,466] and a reduced risk of COPD[438], although the biological function of the *FAM13A* gene is poorly understood. Sequence analysis has indicated that the Rho GTPase activating protein domain is encoded by exons 3-5. This domain has anti-inflammatory activity and tumor suppressor function[467]. Young and colleagues subsequently examined the rs7671167 SNP in *FAM13A* in relation to the risk of both COPD and lung cancer[468]. Their results confirmed the protective effect of the *FAM13A* variant on COPD (allelic OR, 0.79; 95%CI, 0.66-0.96), and showed for the first time that this variant was also associated with lung cancer (allelic OR, 0.64; 95%CI, 0.47-0.87), even in those without COPD (allelic OR, 0.58; 95%CI, 0.38-0.87)[468]. Ziolkowska-Suchanek and colleagues further performed a cumulative genetic risk score analysis based on the three SNPs (rs13180, rs7671167 and rs2568494) in the *FAM13A* gene[469], and revealed that the risk of COPD increased with increasing number of *FAM13A* risk alleles, with an OR of ≥5 risk alleles of 2.998 (95%CI, 1.809-4.968). However, none of the SNPs displayed significant associations with lung cancer in their study[469].

To sum up, GWA studies and candidate gene studies have identified several of the same genetic variants associated with the risk of COPD and lung cancer (Figure 2.6). The SNPs showing strongest association, however, are not necessarily the causal loci; they may just be in linkage disequilibrium with a nearby causal variant. Therefore, further comparisons at the gene expression level within individuals of different genotypes are needed to provide biological evidence for the candidate genes underlying the specific disease.

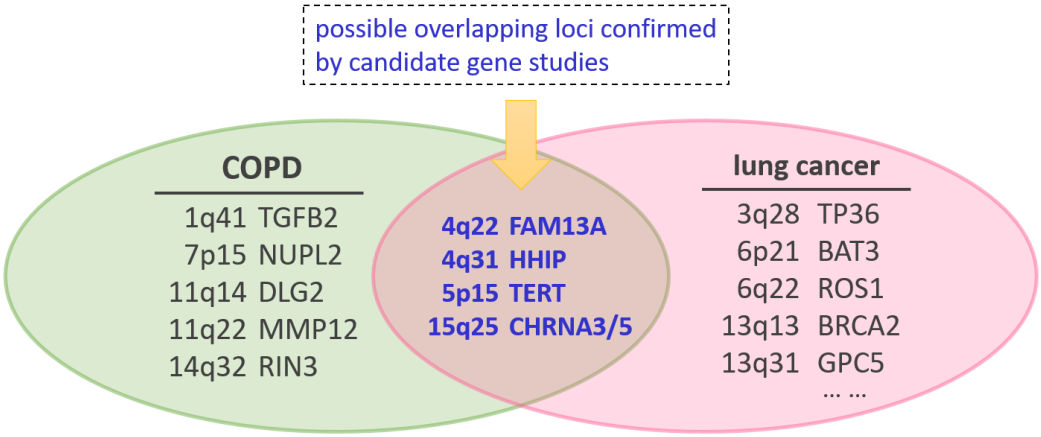


Figure 2.6: Chromosomal loci and associated genes related to COPD and lung cancer from GWA studies. COPD: chronic obstructive pulmonary disease; GWA: genome-wide association.

2.2.3 Clinical implications and future work

There are a number of important implications stemming from the strong link between COPD and lung cancer at the genetic level[39]. First of all, it is obvious that the identification of genetic variants may help define individuals who are at high risk of disease in the preclinical setting. Incorporation of genetic markers into disease risk models has shown promise in raising predictive performance[462,470]. Young and colleagues attempted to create a gene-based risk model combining 12 SNPs with patient demographics (age, family history of lung cancer, and COPD) for lung cancer susceptibility, and their results showed that the area under the curve (AUC) reached 0.75, with the SNP panel contributing most to the total predictive utility (the AUC of SNPs, 0.68)[471]. Along with the improvement of predictability, knowledge of individual genetic predisposition to a certain illness may also have an advantage in management to mitigate the risk exposure. Smokers who were informed of their gene-based health hazard were more likely to modify their smoking behaviour[421,472]. Preliminary results indicated that genetic testing can motivate up to 30% of smokers to quit[473].

In addition, disease screening strategies can be improved with respect to the

identification of target population and surveillance when genetic information is included within existing programmes. Current recommendations for CT screening for lung cancer are largely based on age, smoking status, family history, and history of lung diseases[474,475]. These criteria preclude young people, who represent 1-3% of all lung cancers[476], from the benefits of screening. For these individuals, gene-based risk testing can identify younger smokers at high risk, promoting them for an earlier referral by the physician for CT imaging[477]. Meanwhile, screening eligible candidates who are considered to be in a higher-risk category based on gene testing might also benefit from closer follow-up[478].

Although much progress in genetic knowledge has been made during the past decade, our ability to process and interpret the results still lag behind the technical capacity to produce tremendous amounts of genomic data[39]. Additionally, ever-increasing genetic variants identified by association studies lead to a plethora of putative biomarkers that lack validation. The mechanisms of action of SNPs also remain to be elucidated[479]. Of more importance is how to translate these research findings into clinical practice in a reasonable and ethical manner, with the ultimate goal to improve the health of the public.

CHAPTER THREE

TIMING OF DIAGNOSIS AND SEVERITY OF COPD IN LUNG CANCER

Chronic obstructive pulmonary disease (COPD) and lung cancer are both smoking-related diseases and pose a huge combined burden on healthcare system worldwide[294,480]. Many studies have documented a close interaction between these two diseases with respect to pathogenetic pathways and clinical manifestations[344,414,481]. COPD is associated with greater risk for lung cancer[246,296,303,409,417,481], and several studies indicate that the strength of this association is dependent on the timing of COPD diagnosis[70,299,305].

Since the implementation of low-dose computed tomography (CT) to screen for lung cancer, more lung cancers are diagnosed at their earlier and curable stages[331]. It has been reported that 40%-66% of early-stage non-small cell lung cancer (NSCLC) patients have concomitant COPD[402,405,408]; however, a significant number of patients were unaware of this comorbid condition[482,483]. The diagnosis of COPD is incidentally made during the clinical assessment of lung cancer in this patient population[483].

The role of COPD in lung cancer prognosis have been widely investigated[128,364,402,405,408,484]. Two recent meta-analyses showed that COPD had a negative impact on survival of lung cancer [406,407]; however, the results suffered from a high level of heterogeneity, mostly subject to lung cancer stage and treatment modality[406,407]. Little is known about the prognostic factors stemming from COPD, and their potential influence, particularly for self-unrecognized COPD, on health-related quality of life (QOL) remains unclear.

Since the timing of COPD diagnosis matters in relation to lung cancer risk, and COPD is generally under-diagnosed in patients with early-stage lung cancer, we set forth to investigate the impact of timing of diagnosis, particularly for incidentally diagnosed COPD, and severity of COPD in the prognosis of stage I NSCLC, and to explore independent risk factors for incidentally diagnosed COPD in this patient population.

3.1 Methods

3.1.1 Patients and data collection

The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board. Detailed procedures of patient enrollment, data collection, and follow-up are described in the Appendix. Between January 2000 and December 2014, a total of 1,986 patients with stage I pathologically-confirmed NSCLC who underwent complete resection were included in this study. All patients had written informed consent.

The diagnosis of COPD was determined by patient's medical records and/or documented airflow limitation (the ratio of post-bronchodilator forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC] of less than 0.7[134]). In this study, patients with COPD were divided into two groups according to the timing of diagnosis: those with 'previous COPD' and those with 'incidental COPD'. Those that have a history that was recorded at least 6 months preceding lung cancer diagnosis are categorized as 'previous COPD', and those without a history of COPD, having been incidentally diagnosed within 6 months of lung cancer, are categorized as 'incidental COPD'. Airflow limitation was graded based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[134]: mild (FEV_1 ≥80% predicted), moderate (50%≤ FEV_1 <80% predicted), and severe COPD (FEV_1 <50% predicted).

Postoperative complications were defined as those occurring during hospitalization or within 30 days of operation[485]. A composite variable termed "any postoperative complications" consisting of any complications recorded for each individual patient was also analyzed. Postoperative QOL was evaluated by the Lung Cancer Symptom Scale (LCSS)[486] within two years after surgery (Table 3.1), and each item was assessed as scales varying from 0 (worst) to 10 (best)[106].

Table 3.1: The Lung Cancer Symptom Scale (patient scale)

1. How is your appetite (appetite)?
2. How much fatigue do you have (fatigue)?
3. How much coughing do you have (cough)?
4. How much shortness of breath do you have (dyspnea)?
5. How much blood do you see in your sputum (hemoptysis)?
6. How much pain do you have (pain)?
7. How bad are your symptoms from lung cancer (lung cancer symptom distress)?
8. How much has your illness affected your ability to carry out normal activities (illness affecting normal activities)?
9. How would you rate your quality of life today (overall QOL)?

3.1.2 Statistical analysis

Data was compared across groups using the chi-square (x^2) test for categorical variables, and the unpaired t-test for continuous variables. Survival curves were generated by the Kaplan-Meier method and differences were assessed by the log-rank test. Cox Proportional Hazard modeling was used to control for confounding variables. The difference of postoperative QOL between groups was assessed using the x^2 test and a clinically important difference was defined as a greater than 1 point. A multivariate logistic regression analysis was performed using backward selection to identify risk factors (i.e., patient's demographics, presenting symptoms, and comorbid disease) for incidental COPD in lung cancer patients. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed by SAS, version 9.3 (SAS Institute).

3.2 Results

The mean age was 68.4±9.9 years and 938 (47.2%) patients were male in this

entire cohort. The diagnosis of COPD was identified in 823 (41.4%) patients, including 549 (66.8%) patients with incidental COPD and 274 (33.2%) with previous COPD (Table 3.2). Both incidental COPD and previous COPD were observed more frequently in older age, male gender, and active smokers compared to non-COPD (all p<0.01). Among individuals who had COPD, patients with incidental COPD were younger and had a higher prevalence of current smokers compared to those with previous COPD (both p<0.01). Squamous cell carcinoma was more commonly seen in the setting of COPD, regardless of the timing of COPD diagnosis (both p<0.01). Patients with incidental COPD had a relatively better pulmonary function than those with previous COPD, with statistically significant differences in FEV_1, FEV_1% and FEV_1/FVC (all p<0.05).

Table 3.2: Patient demographics and clinical characteristics (N=1986)

	non-COPD	COPD					p¶
		all	incidental	p#	previous	p#	
No. of patients	1163 (58.6)	823 (41.4)	549 (27.6)		274 (13.8)		
Age (years)	66.8±10.5	70.7±8.6	70.1±8.9	**<0.01**	72.0±7.9	**<0.01**	**<0.01**
Sex				**<0.01**		**<0.01**	0.64
male	494 (42.5)	444 (53.9)	293 (53.4)		151 (55.1)		
female	669 (57.5)	379 (46.1)	256 (46.6)		123 (44.9)		
BMI	27.6±5.6	27.3±5.5	27.0±5.5	**0.05**	27.7±5.3	0.40	**0.03**
Smoking status				**<0.01**		**<0.01**	**<0.01**
never	303 (26.1)	38 (4.6)	27 (4.9)		11 (4.0)		
former	577 (49.6)	497 (60.4)	305 (55.6)		192 (70.1)		
current	283 (24.3)	288 (35.0)	217 (39.5)		71 (25.9)		
Pack years	42.3±28.3	56.1±31.4	55.4±30.8	**<0.01**	57.3±32.5	**<0.01**	0.54
Cell type				**<0.01**		**<0.01**	0.08
ADC	888 (76.4)	494 (60.0)	343 (62.5)		151 (55.1)		
squamous	180 (15.5)	278 (33.8)	171 (31.1)		107 (39.1)		
other NSCLC	95 (8.2)	51 (6.2)	35 (6.4)		16 (5.8)		
Tumor grade				**<0.01**		**<0.01**	0.18
well	487 (41.9)	220 (26.7)	153 (27.9)		67 (24.5)		
moderate	455 (39.1)	437 (53.1)	279 (50.8)		158 (57.7)		
poorly	221 (19.0)	166 (20.2)	117 (21.3)		49 (17.9)		

Table 3.2: Patient demographics and clinical characteristics (N=1986)

	non-COPD	COPD					p¶
		all	incidental	p#	previous	p#	
Stage				0.08		0.84	0.31
IA	801 (68.9)	542 (65.9)	355 (64.7)		187 (68.2)		
IB	362 (31.1)	281 (34.1)	194 (35.3)		87 (31.8)		
FEV_1 (L)	2.6±0.7	1.9±0.6	1.9±0.6	**<0.01**	1.8±0.6	**<0.01**	**0.02**
FEV_1% predicted	94.5±15.7	67.9±17.4	69.5±16.9	**<0.01**	64.5±18.1	**<0.01**	**<0.01**
FEV_1/FVC	77.6±4.8	58.4±9.8	59.1±9.0	**<0.01**	57.0±11.1	**<0.01**	**0.01**
DLCO	19.4±5.5	16.1±5.2	16.2±5.2	**<0.01**	15.7±5.3	**<0.01**	0.21
DLCO% predicted	84.6±17.3	69.4±19.2	70.0±18.6	**<0.01**	68.2±20.1	**<0.01**	0.24

Values are mean ± standard deviation or number (%). #compared with non-COPD; ¶comparison between incidental COPD and previous COPD. COPD: Chronic obstructive pulmonary disease; BMI: body mass index; ADC: adenocarcinoma; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusion capacity of lung for carbon monoxide; NSCLC: non-small cell lung cancer. Bold values indicate P values with statistically significant difference.

3.2.1 Presenting symptoms and comorbid diseases

The presenting symptoms at lung cancer diagnosis differed significantly between incidental COPD and non-COPD in terms of cough, dyspnea and hemoptysis (all p<0.01; Table 3.3). To note, a history of lung infection was also more common in patients with incidental COPD compared to those without COPD (p=0.03).

Table 3.3: Presenting symptoms and comorbid diseases

	non-COPD	incidental COPD		previous COPD		p¶
	n (%)	n (%)	p#	n (%)	p#	
Symptoms						
cough	184 (15.8)	124 (22.6)	**<0.01**	60 (21.9)	**0.02**	0.82
dyspnea	103 (8.9)	82 (14.9)	**<0.01**	38 (13.9)	**0.01**	0.68
sputum	58 (5.0)	36 (6.6)	0.18	13 (8.4)	**0.03**	0.33
chest pain	47 (4.0)	16 (2.9)	0.25	8 (2.9)	0.38	0.99
fatigue	46 (4.0)	21 (3.8)	0.89	12 (4.4)	0.75	0.70

Table 3.3: Presenting symptoms and comorbid diseases

	non-COPD	incidental COPD		previous COPD		p¶
	n (%)	n (%)	p#	n (%)	p#	
back pain	20 (1.7)	3 (0.5)	0.05	1 (0.4)	0.09	0.72
hemoptysis	16 (1.4)	20 (3.6)	**<0.01**	9 (3.3)	**0.03**	0.79
Comorbidities						
other cancer history	268 (23.0)	114 (20.8)	0.29	70 (25.5)	0.38	0.12
previous lung infection	126 (10.8)	79 (14.4)	**0.03**	63 (23.0)	**<0.01**	**<0.01**
diabetes	92 (7.9)	43 (7.8)	0.95	29 (10.6)	0.15	0.19
heart disease	183 (15.7)	92 (16.8)	0.59	61 (22.3)	**<0.01**	0.06
hypertension	288 (24.8)	137 (25.0)	0.93	86 (31.4)	**0.02**	0.05

#compared with non-COPD; ¶comparison between incidental COPD and previous COPD.

COPD: Chronic obstructive pulmonary disease;

Bold values indicate P values with statistically significant difference.

Among patients with COPD, the symptoms and comorbid conditions were similar between patients with incidental COPD and those with previous COPD; however, previous lung infection was more frequently noted in previous COPD (Table 3.3).

3.2.2 Perioperative outcomes

The distribution of type of surgical procedure differed significantly between groups (Table 3.4). Segmentectomy and wedge resection were performed more often in COPD groups than non-COPD group. Furthermore, patients with previous COPD were more likely to receive sublobar resections as compared to those with incidental COPD ($p<0.01$). The rate of any postoperative complications was significantly higher in COPD groups (incidental COPD: 28.1%, previous COPD: 27.0%) than in non-COPD group (16.5%). Specifically, incidental COPD was associated with higher incidence of atrial fibrillation (12.9% vs. 8.5%, $p<0.01$), postoperative pneumonia (3.8% vs. 1.8%, $p=0.01$), and prolonged air leak (12.9% vs. 6.0%, $p<0.01$) as compared to non-COPD. Previous COPD was also associated with prolonged air leak (13.1%, $p<0.01$). There was

no significant difference in postoperative complications between incidental COPD and previous COPD (Table 3.4). The perioperative mortality rate was 1.3% in incidental COPD patients and 0.7% in previous COPD patients, whereas it was 0.5% in non-COPD patients (no significant difference).

Table 3.4: Type of surgical procedure and postoperative complications

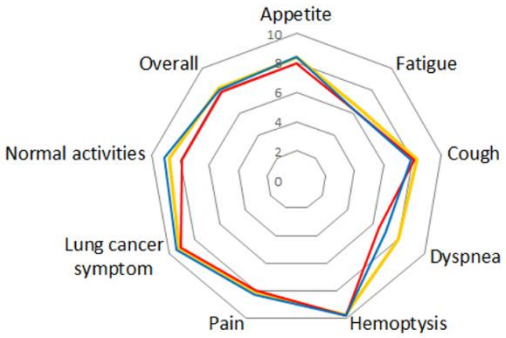
	non-COPD	incidental COPD		previous COPD		p¶
	n (%)	n (%)	p#	n (%)	p#	
Surgical type			**<0.01**		**<0.01**	**<0.01**
wedge resection	220 (18.9)	137 (25.0)		88 (32.1)		
segmentectomy	58 (5.0)	57 (10.4)		47 (17.2)		
lobectomy	885 (76.1)	355 (64.6)		139 (50.7)		
Any postoperative complications	192 (16.5)	154 (28.1)	**<0.01**	74 (27.0)	**<0.01**	
atrial fibrillation	99 (8.5)	71 (12.9)	**<0.01**	32 (11.7)	0.10	0.61
pneumonia	21 (1.8)	21 (3.8)	**0.01**	10 (3.6)	0.06	0.90
prolonged air leak	70 (6.0)	71 (12.9)	**<0.01**	36 (13.1)	**<0.01**	0.93
empyema	2 (0.2)	0 (0.0)	0.33	1 (0.4)	0.53	0.16
chylothorax	16 (1.4)	5 (0.9)	0.41	3 (1.1)	0.71	0.80
DVT/PE	5 (0.4)	1 (0.2)	0.42	1 (0.4)	0.88	0.62
Perioperative mortality	6 (0.5)	7 (1.3)	0.09	2 (0.7)	0.67	0.48

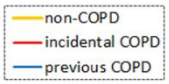
#compared with non-COPD; ¶comparison between incidental COPD and previous COPD.
DVT/PE: deep vein thrombosis/pulmonary embolism; COPD: Chronic obstructive pulmonary disease. "Any postoperative complications" consisted of any complications recorded for each individual patient. Bold values indicate P values with statistically significant difference.

3.2.3 Health-related quality of life

Analysis of health-related QOL found no remarkable difference in overall QOL score between non-COPD and incidental COPD (8.2±1.8 vs. 7.9±1.9). Among specific symptom subscales, dyspnea symptoms were worse in patients with incidental COPD than in those without COPD (6.5±2.4 vs. 8.0±2.4). Similar results were noticed

between non-COPD and previous COPD (Figure 3.1).





	non-COPD	incidental COPD	previous COPD
Appetite	8.4±1.7	8.0±1.8	8.4±1.7
Fatigue	6.5±2.3	6.2±2.4	6.2±2.6
Cough	8.3±1.8	8.1±1.9	7.9±2.2
Dyspnea	8.0±2.4	6.5±2.4#	7.0±2.5#
Hemoptysis	9.8±0.6	9.8±0.4	9.8±0.2
Pain	8.1±2.2	8.0±2.3	8.0±2.3
Lung cancer symptom	9.2±1.5	9.1±1.4	8.8±1.9
Normal activities	8.8±1.7	7.9±2.2	8.4±2.2
Overall	8.2±1.8	7.9±1.9	8.1±1.9

Figure 3.1: Comparison of postoperative quality of life among non-COPD, incidental COPD and previous COPD. (Outer circle representing a higher score and better quality of life; #comparison with non-COPD: $p<0.05$ and difference ≥1 point)

3.2.4 Long-term overall survival

In regard to the severity of COPD, 218 (26.5%) patients had mild, 478 (58.1%) moderate, and 127 (15.4%) severe airflow limitation. Kaplan-Meier curves show that patients with COPD have worse overall survival than those without ($p<0.01$), and the survival difference is independent of the timing of COPD diagnosis. Additionally, there was a more apparent decrease in survival as severity of airflow limitation increased ($p<0.01$, Figure 3.2).

In the multivariate Cox proportional hazard model adjusting for patient demographics and tumor characteristics (Table 3.5), COPD was significantly associated with decreased overall survival (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.06-1.42), which was mainly owing to incidental COPD (HR, 1.23; 95%CI, 1.05-1.45). The impact of previous COPD was on the borderline of statistical significance (HR, 1.20; 95%CI, 0.98-1.46). When COPD cases were stratified based on airflow limitation, the HR was statically significant for moderate (HR, 1.22; 95%CI, 1.04-1.44) and severe COPD (HR, 1.75; 95%CI, 1.38-2.23), but not for mild COPD (HR, 0.99; 95%CI, 0.79-1.23).

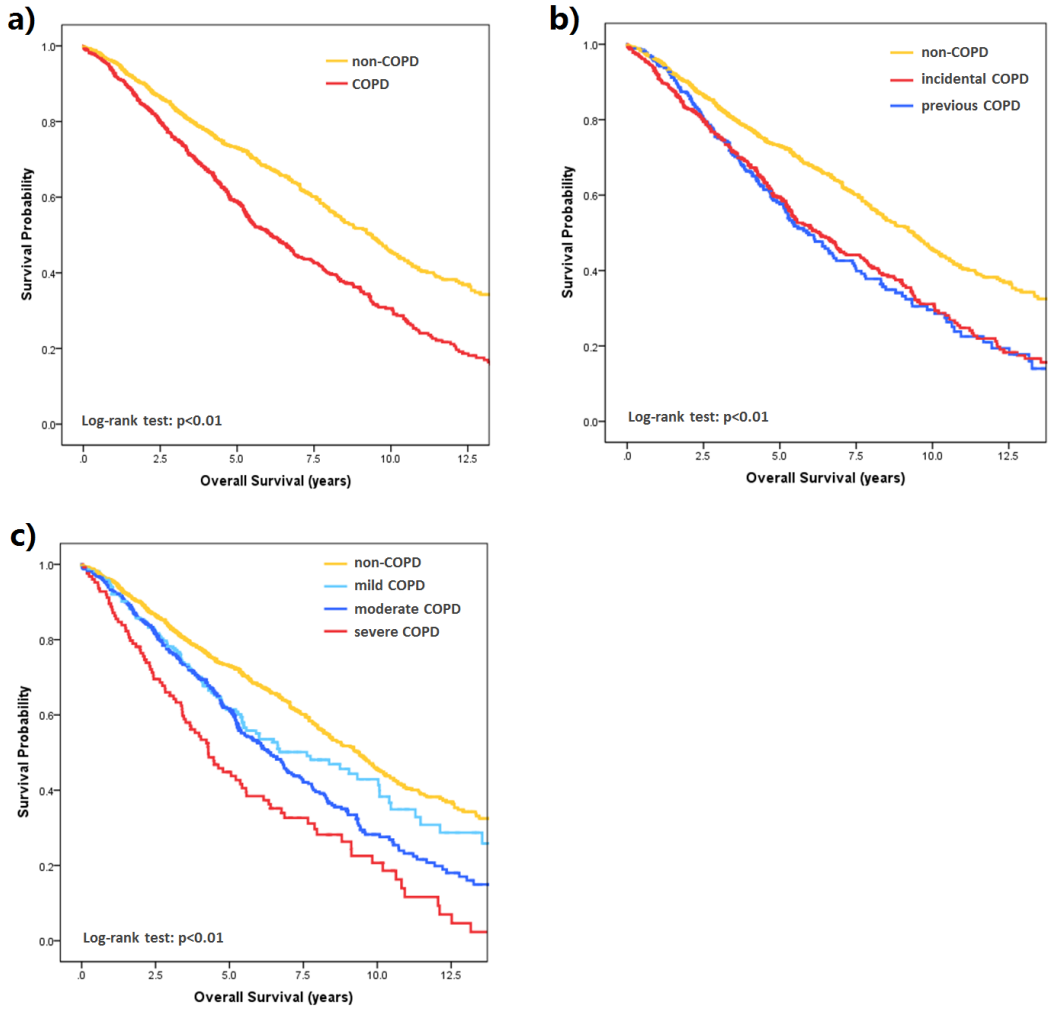


Figure 3.2: Kaplan-Meier curves for overall survival. a) comparison between COPD and non-COPD; b) comparison among non-COPD, incidental COPD and previous COPD; c) comparison between non-COPD and the severity of COPD regardless of timing of diagnosis.

3.2.5 Risk factors for lung cancer with incidental COPD

To further characterize lung cancer cases with an incidental COPD, multivariate logistic regression analysis revealed that older age (odds ratio [OR], 1.04), male gender (OR, 1.30), lower body mass index ([BMI]; OR, 0.97), former and current smokers (OR for former smoker, 4.86; OR for current smoker, 9.02), presenting cough (OR, 1.44), dyspnea (OR, 1.68) and hemoptysis (OR, 2.63) were significant risk factors for having an incidental diagnosis of COPD in newly-diagnosed lung cancer patients (Table 3.6).

Table 3.5: Multivariate Cox proportional hazard model for overall survival

	COPD status		Timing of diagnosis		Severity	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
All COPD*	1.22 (1.06, 1.42)	**0.01**	--		--	
Timing*						
incidental	--		1.23 (1.05, 1.45)	**0.01**	--	
previous	--		1.20 (0.98, 1.46)	0.07	--	
severity*						
mild	--		--		0.99 (0.79, 1.23)	0.91
moderate	--		--		1.22 (1.04, 1.44)	**0.02**
severe	--		--		1.75 (1.38, 2.23)	**<0.01**
Age	1.05 (1.04, 1.06)	**<0.01**	1.05 (1.04, 1.06)	**<0.01**	1.05 (1.04, 1.06)	**<0.01**
Sex						
male	reference		reference		reference	
female	0.75 (0.65, 0.87)	**<0.01**	0.75 (0.65, 0.87)	**<0.01**	0.76 (0.66, 0.87)	**<0.01**
BMI	0.98 (0.97, 1.00)	**0.03**	0.98 (0.97, 1.00)	**0.03**	0.98 (0.96, 1.00)	**0.04**
Smoking						
never	reference		reference		reference	
former	1.34 (1.05, 1.70)	**0.02**	1.34 (1.05, 1.70)	**0.02**	1.33 (1.04, 1.69)	**0.02**
current	1.84 (1.42, 2.38)	**<0.01**	1.83 (1.42, 2.37)	**<0.01**	1.81 (1.40, 2.34)	**<0.01**
Cell type						
ADC	reference		reference		reference	
squamous	1.03 (0.87, 1.22)	0.73	1.03 (0.87, 1.22)	0.72	1.02 (0.86, 1.21)	0.82
other NSCLC	1.50 (1.16, 1.93)	**<0.01**	1.49 (1.16, 1.93)	**<0.01**	1.49 (1.15, 1.92)	**<0.01**
Tumor grade						
well	reference		reference		reference	
moderate	1.46 (1.22, 1.74)	**<0.01**	1.46 (1.22, 1.74)	**<0.01**	1.44 (1.21, 1.72)	**<0.01**
poorly	1.65 (1.32, 2.05)	**<0.01**	1.65 (1.32, 2.05)	**<0.01**	1.67 (1.34, 2.08)	**<0.01**
Stage						
IA	reference		reference		reference	
IB	1.32 (1.15, 1.52)	**<0.01**	1.32 (1.15, 1.52)	**<0.01**	1.32 (1.15, 1.52)	**<0.01**

*Patients without COPD were used as reference group. COPD: Chronic obstructive pulmonary disease; BMI: body mass index. ADC: adenocarcinoma. HR: hazard ratio; CI: confidence interval.

3.3 Discussion

Our investigation revealed a high prevalence of incidentally-diagnosed COPD among patients with stage I NSCLC. Similar to previous COPD, the presence of incidental COPD was associated with postoperative complications and poor health-related QOL. Moreover, COPD significantly decreased overall survival, likely attributable to incidental COPD. Older age, male sex, lower BMI, being former and current smokers, and presenting cough, dyspnea, and hemoptysis were independent predictors for incidental COPD in patients with stage I NSCLC.

In the clinical setting, COPD is often concomitant with primary lung cancer but remains substantially underdiagnosed[402,405]. Our survey revealed that incidental COPD (within 6 months at lung cancer diagnosis) was present in two-thirds of spirometry-defined COPD in lung cancer patients, which was a bit lower to the reported rates of undiagnosed COPD in the surveys of general population (approximately 71.2%-81.4%).[155,156] It is possibly due to the different study design that we only included surgical patients who were more likely to have good lung function.

Table 3.6: Logistic regression analysis to predict incidental COPD in lung cancer patients

	OR	95% CI	p-value
Age	1.04	(1.03, 1.05)	<0.01
Sex (male)	1.30	(1.04, 1.64)	0.02
Body mass index	0.97	(0.95, 0.99)	0.02
Smoking status			
never	reference		
former	4.86	(3.16, 7.49)	<0.01
current/ever	9.02	(5.75, 14.15)	<0.01
Cough	1.44	(1.06, 1.94)	0.02
Dyspnea	1.68	(1.16, 2.43)	<0.01
Hemoptysis	2.63	(1.24, 5.57)	0.01

OR: odds ratio; CI: confidence interval.

Previous case-control studies have shown that the association between COPD and

lung cancer development was more significant when a diagnosis of COPD was chronologically close to the diagnosis of lung cancer[70,305]. However, to the best of our knowledge, its prognostic effect has not been studied before. We therefore targeted patients with surgically resected stage I NSCLC, for the purpose of eliminating the potential survival bias caused by lung cancer stage and treatment[407]. The results showed that COPD was significantly associated with worse overall survival, mainly owing to incidental COPD.

The exact mechanisms by which incidental COPD worsen lung cancer survival have not been clearly elucidated thus far. Several hypotheses have been proposed, such as uncontrolled inflammation and tendency to continued smoking in these patients. COPD is characterized by chronic neutrophilic inflammation[134,487] that could stimulate angiogenesis and promote tumor metastasis[488,489], which has been demonstrated to be inversely correlated with early-stage lung cancer outcomes[104,490,491]. Pharmacological treatment for COPD, represented by inhaled bronchodilators and corticosteroids[492], can attenuate airway inflammation and reduce the level of some markers of systemic inflammation[317,493]. Zhang and colleagues found that lung cancer patients with documented diagnosis of COPD were more likely to receive medications for COPD while those with incidental COPD were mostly under-treated[483]. Therefore, patients with stage I NSCLC who have an incidental diagnosis of COPD may suffer from the persistent uncontrolled inflammation, contributing to poorer lung cancer survival. In addition, early COPD diagnosis may motivate smoking cessation[494], which is the most effective measure to improve future prospects for the patients[480,495]. As shown in our study, current smokers were more commonly seen in lung cancer patients with incidental COPD compared to both non-COPD and previous COPD, which could pose an additional risk of death from lung cancer[496,497]. Therefore, in view of the high prevalence of incidental COPD and its negative impact on lung cancer survival, the timely identification and subsequent effective treatment for COPD are critically important to newly-diagnosed lung cancer patients.

Interestingly, the impact of previous COPD was borderline significant in the multivariate model. This could be due in part to the small group size. On the other hand, Powell and colleagues pointed out that COPD which was diagnosed long before (at least 6 months interval) the diagnosis of lung cancer was not necessarily directly associated with lung cancer; rather the association was possibly due to a patient's smoking habit[305]. Furthermore, COPD diagnosed within short time windows may reflect the COPD status in a more accurate way. This association will need to be confirmed by larger studies.

When COPD was stratified by severity of airflow limitation, survival was similar in patients with mild COPD and patients without COPD, whereas moderate-to-severe COPD was significantly associated with worse outcome. This result is concordant with Qiang and colleagues[484], who reported an apparent decrease in recurrence-free survival in NSCLC patients with moderate/severe COPD but not in those with mild COPD.

Postoperative QOL was also associated with incidental COPD, mainly in dyspnea subscale. This result is in contrast to the study from Pompili and colleagues[411], who reported no difference with regard to COPD status; however, disparities in the study design, targeted population and type of survey make comparison uncertain. Our study only included stage I NSCLC and showed that patients with incidental COPD tended to be older and active smokers. Ferguson and colleagues found that lung cancer patients aged ≥70 years experienced worse dyspnea than those <70 years after major lung resection[498]. In addition, a recent systematic review demonstrated that cigarette smoking was often associated with an increase in symptom burden[499]. These factors could predispose COPD patients to poorer QOL. Accordingly, lung cancer patients with incidental COPD should also be given rigorous interventions (e.g., pulmonary rehabilitation) to promote disease recovery and improve their long-term QOL, as is generally suggested in those with previously recognized COPD[481].

COPD is considered as an independent risk factor for postoperative complications[500]. Our study demonstrated that patients with incidental COPD had a higher incidences of overall postoperative complication than those without, with significant differences noted in atrial fibrillation, pneumonia, and prolonged air leak. These findings highlighted the importance of identification of “insidious” COPD for an accurate surgical risk assessment.

Although concurrent diseases should be detected in patients with lung cancer, no consensus exists on how and when to systemically screen for comorbidities. In addition, given patients with COPD are at higher risk for developing lung cancer, early detection of COPD would be important for lung cancer surveillance[296,417]. However, our data shows that approximately two-thirds of subjects with COPD were incidentally diagnosed due to the clinical assessment for lung cancer. As such, recommendation for lung cancer screening in previously-diagnosed subjects with COPD would only benefit a limited population, leaving vast majority of cases underestimated. Hence, we further determine the risk factors for incidental COPD; patient smoking history and respiratory symptoms (cough, dyspnea, and hemoptysis) were the most important risk determinants, which is consistent with previous studies[155,337,501]. Since the US Preventive Services Task Force (USPSTF) recommends against screening for COPD in asymptomatic adults[502,503], our study characterized those who may have undiagnosed COPD, which in turn could improve risk stratification in lung cancer screening in individuals who are already at an increased risk of developing but remain unrecognized. This might have both cost and prognostic implications.

The major strength of our study is to record the timing of diagnosis and severity of airflow limitation in all COPD patients. This will allow us to determine the prevalence and impact of incidental COPD in the context of early-stage lung cancer, address the gap in the implementation of active lung cancer screening in COPD patients, and to refine the prognostication in lung cancer cases with varying COPD grades. However, a

number of limitations should be acknowledged. First, although our patient cohort was prospectively followed, this study was retrospective and observational in nature; thus, the potential bias could not be completely eliminated. Second, the 'incidental COPD' was defined arbitrarily by an interval of 6 months between COPD and lung cancer diagnosis. Nevertheless, the prevalence rate of 'incidental COPD' in our study is similar to the reported rates in previous studies[155,482] , justifying this method of grouping to some extent. Third, the treatment for COPD and the cause of death are not available, which limits the ability of the study to assess the effects of treatment-related factors on lung cancer- and COPD-specific mortality. Lastly, the insignificant association for previous COPD and lung cancer survival could be possibly due to lower statistical power as this group is smaller than incidental COPD (274 vs. 549). Therefore, further validation from larger-scale cohorts is warranted to address these issues.

3.4 Chapter Summary

In summary, our study uncovered a substantially high prevalence of incidentally-diagnosed COPD among patients with stage I NSCLC, and demonstrated that timing of diagnosis and severity of COPD mattered with respect to lung cancer prognosis. COPD significantly decreased overall survival, mainly owing to incidental COPD. Moderate and severe COPD negatively affected survival outcome while mild COPD did not. Therefore, the clear identification of COPD status at lung cancer diagnosis is important.

CHAPTER FOUR

ROLE OF REGIONAL EMPHYSEMA IN EARLY STAGE LUNG CANCER OUTCOMES

Chronic obstructive pulmonary disease (COPD) and lung cancer are leading causes of death worldwide[295]. Emphysema is the major component of COPD and has been demonstrated to confer a higher risk of lung cancer, independent of tobacco smoking and airflow obstruction[302,304]. It is reported that more than half of patients with newly diagnosed lung cancer have emphysema[504,505], but the prognostic role of emphysema in lung cancer remains unclear and conflicting[313,345,506,507]. Our previous experience indicates that the local risk of lung cancer was related to severity of regional emphysema[353]; however, the prognostic significance of regional emphysema has not been well characterized. This chapter investigates the impact of the region emphysema scores (RES) on the long-term prognosis of patients with early-stage non-small cell lung cancer (NSCLC) in terms of overall survival (OS), health-related quality of life (QOL), and postoperative recovery of pulmonary function.

4.1 Methods

4.1.1 Subject inclusion

Detailed procedures of patient enrollment, data collection, and follow-up can be found in the Appendix. To ensure patients with at least five-year follow-up appointments, the cohort of patients whose disease was diagnosed between 1997 and 2009 was considered; a total of 1,073 patients met our study inclusion criteria: pathologically-confirmed early-stage NSCLC (stage I-II), available standard-dose CT scan before treatment, and provision of written informed consent.

4.1.2 Patient evaluation

The diagnosis of COPD was determined by patient's medical record and/or

documented irreversible airflow limitation (post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] of less than 70%)[134]. Perioperative mortality was defined as death during hospitalization or within 30 days of operation[485]. Postoperative complications included conditions such as atrial fibrillation, pneumonia, prolonged air leak (more than 7 days), and tracheostomy that occurred during hospitalization or within 30 days following surgery. A composite variable "any postoperative complications" consisting of any complications recorded (including but not limited to the aforementioned) was generated for each individual patient. Pulmonary function tests (PFT) were performed within half a year before lung cancer treatment and repeated within two years after pulmonary resection. The values of FEV_1/FVC, percentage of FEV1 (FEV_1%), residual volume (RV), total lung capacity (TLC), and diffusion capacity of lung for carbon monoxide (DLCO) were evaluated and expressed as the changes from preoperative to postoperative evaluation. QOL was assessed using the Lung Cancer Symptom Scales[486] within two years after treatment, and each item was scored on a scale of 0-worst to 10-best[106].

4.1.3 Computed tomography scan

CT scans were performed using helical CT scanner (General Electric Medical Systems, Milwaukee, WI, USA)[309]. CT examinations extended in a craniocaudal direction, without intravenous contrast material. The technical scan parameters included the following: tube voltage, 120 kV; tube current, 40 mA; 5 mm section width with 3.5-3.75 mm reconstruction interval; and high-speed mode[309,508]. The CT images of the entire lung region were obtained in a single breath hold at full inspiration. All images were viewed by an experienced thoracic radiologist, who was blinded to all clinical data, at standard lung (width, 1500HU; level, -600HU), soft tissue (width, 400HU; level, 40HU), and bone (width, 1000 HU; level, 200HU) window settings[508].

4.1.4 Emphysema evaluation

Emphysema evaluation was based on a standard-dose CT before treatment. Patients with a low-dose CT only were excluded. The severity of emphysema was scored through direct interpretation under computer-aided quantitative standard images that were generated by using -950HU as the threshold for emphysema[312,353]. The extent of emphysema was given to each of six lung zones: right and left lung, upper, middle (or lingula), and bilateral lower lobes. Individual RESs were derived from the emphysematous region and classified as follows: mild (≤5%), moderate (6-24%) and severe (25-60%). Patients were then divided into three groups according to the tumor location and treatment modality (Figure 4.1): lung cancer in emphysematous (group 1, n=565) and non-emphysematous (group 2, n=435) regions with surgical resection and lung cancer with non-surgical treatment (group 3, n=73).

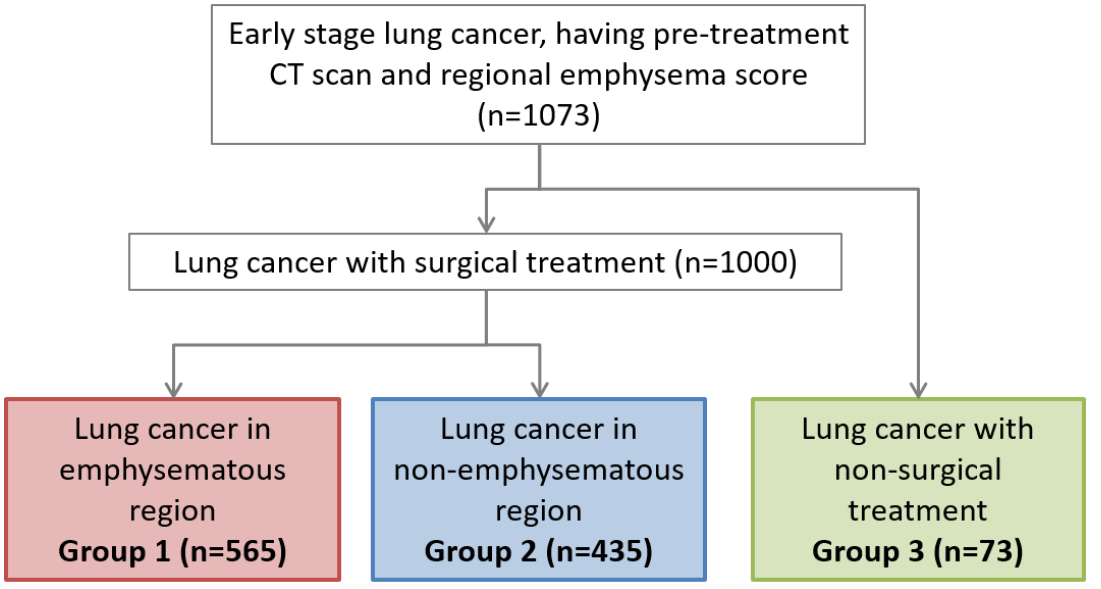


Figure 4.1: Study population.

The frequencies of mild, moderate and severe RES were 63.0%, 26.6%, and 10.4% in group 1 (surgically treated cancer in the emphysematous region), 71.7%, 19.8%, and 8.5% in group 2 (surgically treated cancer in the non-emphysematous region). In group 3 (non-surgically treated cancer), the frequency of RES was in a similar distribution

(50.7% mild, 37% moderate and 12.3% severe) but the small numbers (total of 73 patients) meant that severe and moderate RES were combined for subsequent analysis.

4.1.5 Statistical analysis

Clinical data were compared using the chi-square (x^2) test, or the Fisher exact text (as appropriate) for categorical variables, and the unpaired t-test for continuous variables. Survival curves were generated by the Kaplan-Meier method and differences were assessed by the log-rank test. Cox proportional hazards models were used to evaluate the association between RES and OS after adjusting for patient's demographics, tumor stage and treatment, and COPD status. The difference in QOL between groups was assessed by using the x^2 test and a clinically important difference was defined as a greater than 1 point. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with SAS, v9.3 (SAS Institute).

4.2 Results

4.2.1 Baseline clinical features

Patient demographic and clinical characteristics are listed in Table 4.1. In all groups, moderate and severe RESs were noted more frequently than mild RESs in patients who were former or current smokers and had smoked for more pack-years ($p<0.05$). Coexistence of COPD was significantly more frequent in patients with a higher RES ($p<0.01$).

Table 4.1: Patient demographics and clinical characteristics by tumor location and regional emphysema score

RES	Group 1			Group 2			Group 3		Total
	mild	moderate	severe	mild	moderate	severe	mild	moderate/severe	
Gender									
male	176 (49.4%)	98 (65.3%)	35 (59.3%)*	147 (47.1%)	56 (65.1%)	19 (51.4%)*	19 (51.4%)	17 (47.2%)	567 (52.8%)
female	180 (50.6%)	52 (34.7%)	24 (40.7%)	165 (52.9%)	30 (34.9%)	18 (48.6%)	18 (48.6%)	19 (52.8%)	506 (47.2%)
Age (years)	67.6±9.6	68.6±7.7	68.2±8.0	66.8±10.1	69.4±7.2	71.5±7.1**	72.1±8.2	71.3±7.9	68.1±9.2
Smoking status									
never	63 (17.7%)	1 (0.7%)	0 (0.0%)**	77 (24.7%)	2 (2.3%)	0 (0.0%)**	5 (13.5%)	0 (0.0%)*	148 (13.8%)
former	207 (58.1%)	80 (53.3%)	35 (59.3%)	177 (56.7%)	57 (66.3%)	27 (73.0%)	26 (70.3%)	25 (69.4%)	634 (59.1%)
current	86 (24.2%)	69 (46.0%)	24 (40.7%)	58 (18.6%)	27 (31.4%)	10 (27.0%)	6 (16.2%)	11 (30.6%)	291 (27.1%)
pack×year	46.0±31.1	59.5±32.2	66.6±33.0**	45.0±31.4	58.1±27.4	52.8±27.6**	50.6±39.8	65.4±33.4*	51.5±32.2
BMI	27.8±5.0	26.5±4.6	25.0±5.0**	28.4±5.7	26.4±4.7	25.5±4.4**	28.6±5.6	26.6±5.5	27.5±5.3
COPD									
no	206 (57.9%)	33 (22.0%)	5 (8.5%)**	181 (58.0%)	16 (18.6%)	4 (10.8%)**	13 (35.1%)	2 (5.6%)**	460 (42.9%)
yes	150 (42.1%)	117 (78.0%)	54 (91.5%)	131 (42.0%)	70 (81.4%)	33 (89.2%)	24 (64.9%)	34 (94.4%)	613 (57.1%)
Histology									
adenocarcinoma	240 (67.4%)	84 (56.0%)	22 (37.3%)**	181 (58.0%)	42 (48.8%)	18 (48.6%)**	16 (43.2%)	11 (30.6%)	614 (57.2%)
squamous	79 (22.2%)	55 (36.7%)	28 (47.5%)	59 (18.9%)	36 (41.9%)	13 (35.1%)	13 (35.1%)	15 (41.7%)	298 (27.8%)
other NSCLC	37 (10.4%)	11 (7.3%)	9 (15.3%)	72 (23.1%)	8 (9.3%)	6 (16.2%)	8 (21.6%)	10 (27.8%)	161 (15.0%)
Tumor grade									
well	138 (38.8%)	35 (23.3%)	8 (13.6%)**	112 (35.9%)	21 (24.4%)	6 (16.2%)**	7 (18.9%)	4 (11.1%)	311 (30.8%)
moderately	152 (42.7%)	86 (57.3%)	31 (52.5%)	113 (36.2%)	53 (61.6%)	23 (62.2%)	14 (37.8%)	15 (41.7%)	487 (45.4%)
poorly	66 (18.5%)	29 (19.3%)	20 (33.9%)	87 (27.9%)	12 (14.0%)	8 (21.6%)	16 (43.2%)	17 (47.2%)	255 (23.8%)
Stage									
Ia	208 (58.4%)	70 (46.7%)	25 (42.4%)**	160 (51.3%)	39 (45.3%)	24 (64.9%)	11 (29.7%)	13 (36.1%)	550 (51.3%)
Ib	88 (24.7%)	44 (29.3%)	14 (23.7%)	73 (23.4%)	21 (24.4%)	9 (24.3%)	6 (16.2%)	8 (22.2%)	263 (24.5%)
IIa	26 (7.3%)	19 (12.7%)	6 (10.2%)	46 (14.7%)	13 (15.1%)	3 (8.1%)	4 (10.8%)	3 (8.3%)	120 (11.2%)
IIb	34 (9.6%)	17 (11.3%)	14 (23.7%)	33 (10.6%)	13 (15.1%)	1 (2.7%)	16 (43.2%)	12 (33.3%)	140 (13.0%)

*p<0.05, **p<0.01; RES: regional emphysema score; BMI: body mass index; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease.

Of the 1,000 patients receiving surgical resection (group 1 and group 2), lobectomy was performed in 782 (78.2%) patients, segmentectomy in 68 (6.8%), and wedge resection in 150 (15.0%). No significant difference was found in the distribution of type of surgical procedure between the two groups (p=0.73). In group 3, the patients with non-surgical treatment, 34 (46.6%) received radiation, 27 (37.0%) underwent chemotherapy/chemoradiotherapy, and the remaining 12 (16.4%) had other supportive treatment.

In surgically-treated patients (group 1 and group 2), the preoperative PFT results are summarized in Table 4.2. As expected, with higher RESs, there was evidence of greater airflow obstruction, lower diffusion capacity and more marked hyperinflation.

Table 4.2: Preoperative pulmonary function (group 1 and group 2)

RES	group 1			group 2		
	mild	moderate	severe	mild	moderate	severe
FEV_1 (L)	2.4±0.7	2.1±0.8	1.8±0.7**	2.3±0.7	2.2±0.7	1.6±0.7**
FEV_1%	84.0±19.4	69.6±21.9	60.0±19.6**	83.0±20.5	71.2±17.2	60.7±22.5**
FEV_1/FVC	71.5±9.6	58.6±12.5	51.5±11.2**	71.1±11.0	61.2±12.1	51.2±14.7**
TLC (L)	6.1±1.2	7.1±1.4	7.1±1.3**	6.2±1.3	6.8±1.6	6.8±1.4*
TLC%	104.0±14.2	114.9±15.9	118.3±13.7**	102.6±16.4	108.2±18.4	117.9±17.8**
RV (L)	2.9±0.9	3.7±1.2	3.7±1.0**	2.9±9.5	3.2±1.0	3.8±1.1**
DLCO	20.0±5.8	16.0±5.2	13.9±4.7**	19.8±5.4	16.3±4.5	10.8±3.5**
DLCO%	85.2±19.4	65.6±17.8	57.2±14.1**	85.1±18.5	66.9±15.4	48.2±14.5**

RES: regional emphysema score; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity of lung for carbon monoxide; Comparisons between different emphysema scores in group 1 and group 2: *p<0.05, **p<0.01

Postoperative complications increased in both surgical groups as the RES increased (Table 4.3). Postoperative pneumonia occurred more commonly in patients with a severe RES than in those with a mild to moderate RES in both groups (both p<0.05). In group 1 (cancer in the emphysematous region), the incidence of prolonged air leak was twice as high in patients with a moderate RES and three times as high in

patients with a severe RES than in patients with a mild RES ($p<0.01$). Three patients died during the postoperative course, including 2 of pneumonia and 1 of acute renal failure; however, there was no significant association between the RES and postoperative mortality in either group.

Table 4.3: Postoperative complications in surgically treated patients (group 1 and group 2)

Regional emphysema score	group 1			group 2		
	mild	moderate	severe	mild	moderate	severe
atrial fibrillation	35 (9.8)	20 (13.3)	5 (8.5)	25 (8.0)	11 (12.8)	6 (16.2)
pneumonia	6 (1.7)	7 (4.7)	5 (8.5)*	4 (1.3)	2 (2.3)	3 (8.1)*
prolonged air leak (>7d)	21 (5.9)	16 (10.7)	11 (18.6)**	16 (5.1)	8 (9.3)	4 (10.8)
tracheostomy	2 (0.6)	1 (0.7)	2 (3.4)	1 (0.3)	0 (0.0)	0 (0.0)
any postoperative complications	88 (24.7)	62 (41.3)	29 (49.2)**	74 (23.7)	27 (31.4)	15 (40.5)*
perioperative mortality	0 (0.0)	1 (0.7)	1 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)

Comparisons between different emphysema scores in group 1 and group 2: *$p<0.05$; **$p<0.01$

Operative mortality and complications defined as the event (death or complications) that occurred during hospitalization or within 30 days of the operation. "Any postoperative complications" defined as any complications recorded for each individual patient.

4.2.2 Changes in pulmonary function

After surgery, 152 (26.9%) patients in group 1 and 122 (28.0%) in group 2, had a follow-up PFT, at a mean of 13.4±5.9 months after surgery (range, 3.2 to 23.8 months). In general, some decline in lung function was noticed in both groups. In group 1 (cancer in the emphysematous region) there was a significantly greater decline in lung function (as measured by FEV_1% and DLCO%) in patients with a mild RES than in those with a moderate or severe RES; however, a significant improvement in FEV_1/FVC was observed in patients with a moderate or severe RES (Figure 4.2). These associations were not evident in group 2 (cancer in the non-emphysematous region).

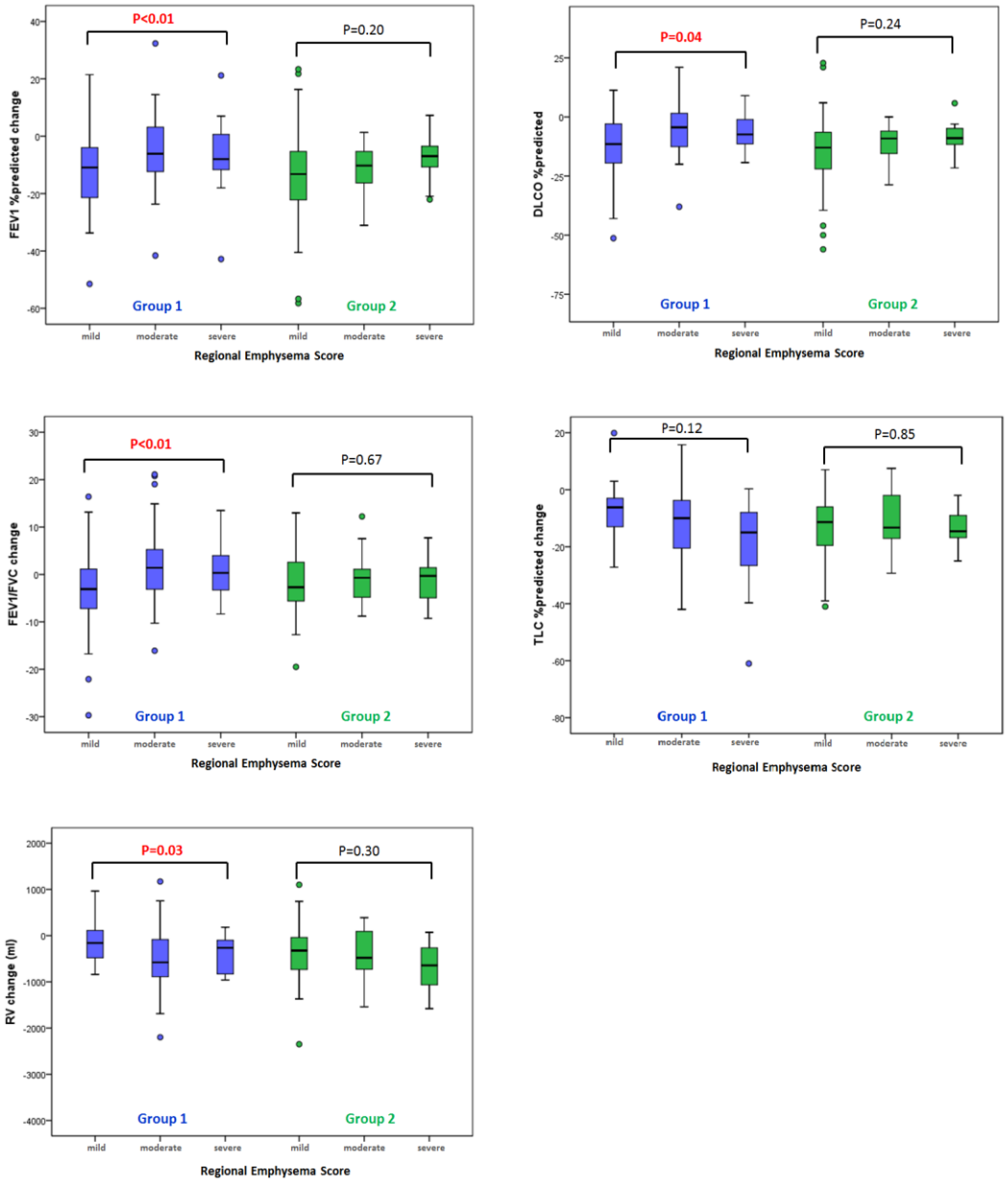


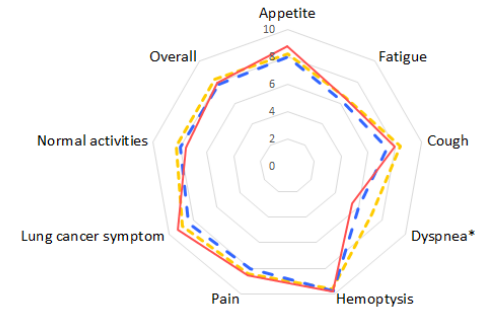
Figure 4.2: Postoperative pulmonary function changes within 2 years. Values were expressed as the changes from preoperative evaluation to postoperative evaluation. Group 1, tumor in emphysematous region; Group 2, tumor in non-emphysematous region.

4.2.3 Post-treatment quality of life

Within two years after treatment, 394 (69.7%) patients in group 1, 322 (74.0%) in group 2, and 54 (74.0%) in group 3 answered the QOL questionnaire. No striking

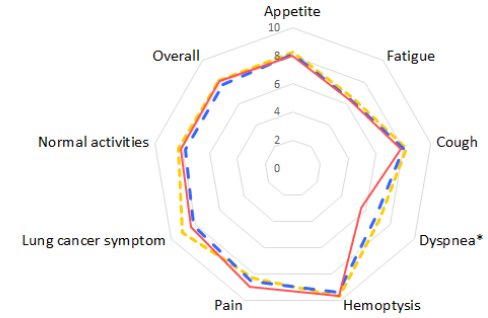
difference in overall QOL was observed between different RES in each group (Figure 4.3). On the specific symptom subscales, dyspnea scores were worse in patients with a severe RES in all groups (all p<0.05 and difference >1 point). In group 3 (cancer with non-surgical treatment), fatigue was worse in patients with a moderate/severe RES than in those with a mild RES, which was independent of non-surgical treatment modalities (p=0.68).

a. Group 1



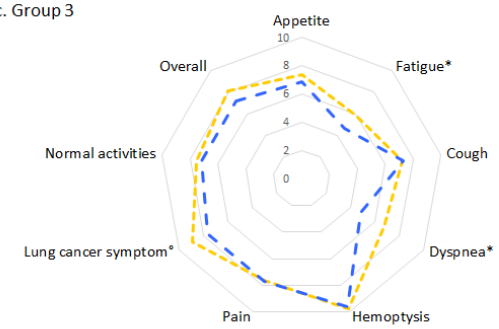
Group 1	mild	moderate	severe
Appetite	8.2±1.8	8.0±1.8	8.8±0.9
Fatigue	6.6±2.3	6.2±2.3	6.5±2.1
Cough	8.4±1.9	7.4±2.4	8.0±2.0
Dyspnea	7.1±2.3	6.0±2.5	5.5±2.0*
Hemoptysis	9.6±0.8	9.8±0.3	9.8±0.2
Pain	8.4±2.0	8.0±2.2	8.5±1.9
Lung cancer symptom	8.9±1.6	8.4±2.2	9.3±0.9
Normal activities	8.3±2.0	8.0±2.0	7.6±1.9
Overall	8.3±1.7	7.8±1.9	8.0±2.0

b. Group 2



Group 2	mild	moderate	severe
Appetite	8.3±1.8	8.1±1.7	8.0±1.6
Fatigue	6.6±2.3	6.4±2.1	6.3±2.0
Cough	8.2±1.8	8.0±2.0	7.8±1.9
Dyspnea	7.2±2.4	6.8±2.3	5.6±2.6*
Hemoptysis	9.7±0.4	9.4±1.3	9.7±0.3
Pain	8.3±1.9	8.6±1.6	9.0±1.6
Lung cancer symptom	9.1±1.4	8.2±2.4	8.4±2.7
Normal activities	8.3±2.0	7.8±2.3	8.1±2.1
Overall	8.2±2.0	7.8±2.2	8.1±1.9

c. Group 3



Group 3	mild	moderate/severe
Appetite	7.4±1.4	6.9±2.6
Fatigue	5.9±2.3	4.7±2.0*
Cough	7.2±2.4	7.3±2.8
Dyspnea	6.7±2.7	4.8±2.7*
Hemoptysis	9.8±0.2	9.6±0.3
Pain	7.6±2.9	7.7±2.6
Lung cancer symptom	8.9±1.2	7.7±3.2
Normal activities	7.5±1.9	7.2±2.3
Overall	8.1±1.8	7.2±2.3

Figure 4.3: Quality of life within 2 years after treatment. (a) lung cancer in emphysematous region with surgical resection; (b) lung cancer in non-emphysematous region with surgical resection; (c) lung cancer with non-surgical treatment. (Outer circle representing a higher score and better quality of life; *p<0.05 and difference >1 point).

4.2.4 Overall survival

The respective 5-year OS rates in patients with mild, moderate and severe RES were 79.6%, 67.8% and 63.8% in group 1; 74.1%, 55.8% and 50.0% in group 2; and 24.3% and 22.2% in patients with mild and moderate/severe RESs in group 3. Kaplan-Meier survival analysis showed significant differences in OS among those with mild, moderate and severe RES in the surgical groups (both p<0.01), but no significant difference between mild and moderate/severe RES in the non-surgical group (p=0.90, Figure 4.4).

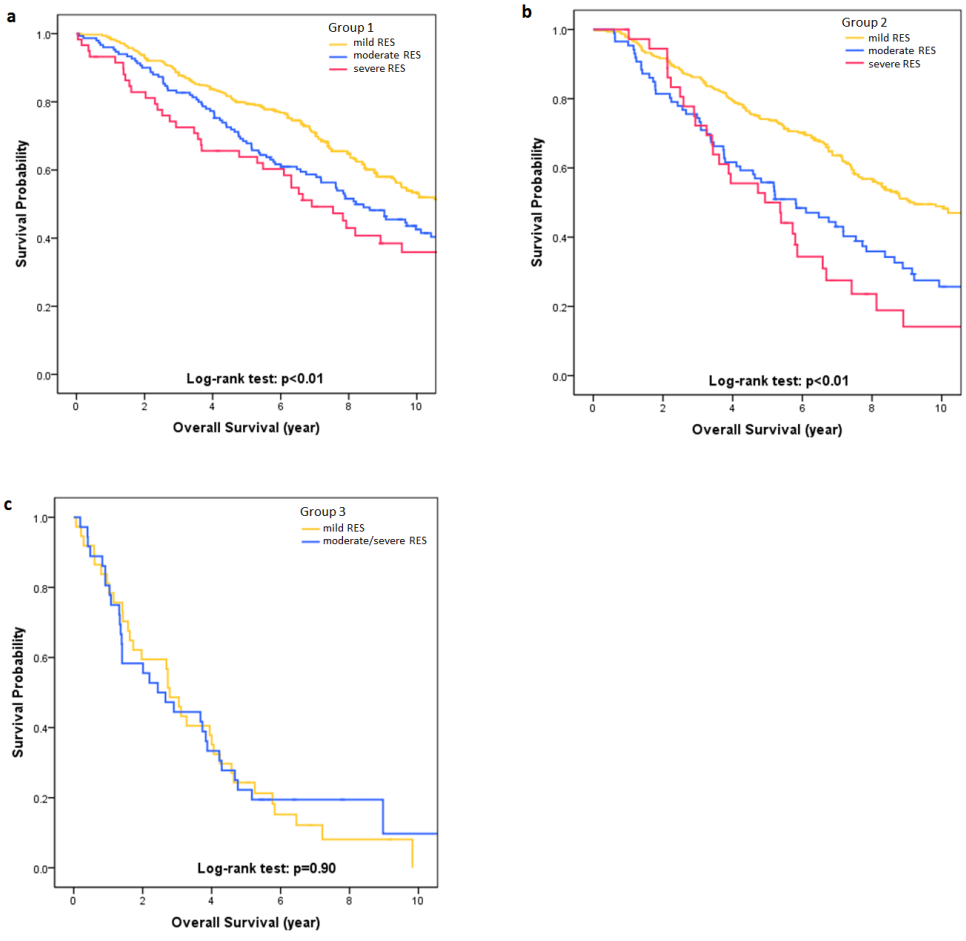


Figure 4.4: Kaplan-Meier curves for overall survival (OS) between different regional emphysema scores (RES) in three groups: (a) lung cancer in emphysematous region with surgical resection; (b) lung cancer in non-emphysematous region with surgical resection; (c) lung cancer with non-surgical treatment.

In multivariate analysis, RES was significantly associated with reduced survival for moderate and severe RES compared with mild RES in group 1 (moderate: HR, 1.41[1.08, 1.84]; severe: HR, 1.63[1.11, 2.38]) and group 2 (moderate: HR, 1.43[1.04, 1.96]; severe: HR, 2.04[1.33, 3.12]). RES was not a prognostic factor in group 3 (Table 4.4).

Table 4.4: Multivariate analysis for overall survival in 3 comparative groups

Variable	group 1		group 2		group 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age		<0.0001		<0.0001		0.2341
	1.06 (1.04,1.08)		1.04 (1.02,1.06)		1.02 (0.98,1.07)	
Gender		0.0064		0.0868		0.0762
Male	reference		reference		reference	
Female	0.71 (0.56,0.91)		0.79 (0.59,1.04)		0.58 (0.31,1.06)	
Body mass index		0.5921		0.5669		0.6854
	0.99 (0.97,1.02)		0.99 (0.97,1.02)		1.01 (0.96,1.07)	
Smoking status		0.2917		0.0922		0.2348
Never	reference		reference		1.21 (0.36,4.09)	
Former	0.85 (0.55,1.31)		1.61 (1.01,2.57)		reference	
Current/ever	1.05 (0.65,1.68)		1.39 (0.81,2.40)		1.84 (0.93,3.66)	
Histology		0.5812		0.6960		0.3155
adenocarcinoma	reference		reference		reference	
squamous	1.06 (0.80,1.40)		0.94 (0.68,1.31)		1.06 (0.43,2.58)	
other NSCLC	0.84 (0.53,1.31)		1.16 (0.74,1.81)		0.56 (0.19,1.69)	
Grade		0.1025		0.4165		0.1073
well	reference		reference		reference	
moderate	1.36 (1.02,1.81)		1.08 (0.77,1.51)		0.54 (0.17,1.68)	
poorly	1.33 (0.92,1.92)		0.83 (0.54,1.29)		1.22 (0.39,3.79)	
COPD		0.9123		0.5060		0.8330
no	reference		reference		reference	
yes	1.01 (0.78,1.32)		1.11 (0.82,1.50)		1.12 (0.38,3.29)	
Stage		0.8101		0.0052		0.4888
Ia	reference		reference		reference	
Ib	1.01 (0.77,1.32)		1.20 (0.88,1.64)		1.04 (0.43,2.52)	
IIa	1.10 (0.73,1.65)		1.79 (1.24,2.59)		1.70 (0.57,5.10)	
IIb	1.20 (0.81,1.77)		1.81 (1.19,2.77)		1.76 (0.77,4.01)	

Table 4.4: Multivariate analysis for overall survival in 3 comparative groups

Variable	group 1		group 2		group 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Surgical treatment		0.0983		0.0216		--
surgery only	reference		reference		--	
surgery+chemotherapy	0.78 (0.46,1.33)		1.49 (0.97,2.30)		--	
surgery+radiation	1.27 (0.67,2.42)		1.69 (0.79,3.61)		--	
surgery+chemoradiation	2.13 (1.12,4.06)		3.58 (1.49,8.63)		--	
Non-surgical treatment		--		--		0.0018
radiation only	--		--		reference	
chemotherapy only	--		--		0.56 (0.16,1.93)	
chemoradiotherapy	--		--		0.43 (0.18,1.02)	
other treatment	--		--		3.04 (1.17,7.94)	
COPD		0.9123		0.5060		0.8330
no	reference		reference		reference	
yes	1.01 (0.78,1.32)		1.11 (0.82,1.50)		1.12 (0.38,3.29)	
RES		0.0095		0.0027		0.9712
mild	reference		reference		reference	
moderate	1.41 (1.08,1.84)		1.43 (1.04,1.96)		0.99 (0.55,1.78)*	
severe	1.63 (1.11,2.38)		2.04 (1.33,3.12)			

*including patients with moderate and severe regional emphysema score.

Group was divided by tumor location and treatment modality: group 1, tumor in the emphysematous region with surgical resection; group 2, tumor in the non-emphysematous region with surgical resection; group 3, tumor with non-surgical treatment.

NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; RES: regional emphysema score.

4.3 Discussion

Emphysema is a frequent coexisting disease in patients with lung cancer and increases postoperative pulmonary morbidities after lung resection[506,509]. Our findings demonstrated that the RES was an independent predictor of OS in early-stage NSCLC after surgery regardless of tumor location, and it was also associated with post-

treatment dyspnea in those with a severe RES versus a mild or moderate RES. Lung function declined postoperatively in both surgical groups, with a significant increase in FEV_1/FVC noted in those with a moderate or severe RES in group 1 (cancer in the emphysematous region).

To date, much attention has been focused on the difference in prognosis between lung cancer arising in emphysematous and non-emphysematous lungs[345]. Several studies[313,507,510] reported an association between the presence of emphysema and lung cancer mortality but others studies[482,506,511]did not support such association after controlling for patient age, gender, smoking history, and cancer stage. In these previous studies, quantification of emphysema was based on whole lung evaluation, without accounting for the regional distribution of emphysema. However, recent studies[353,504] suggest that primary lung cancers arise more frequently in regional areas of worse emphysematous change. We therefore hypothesized that RES may have prognostic value in lung cancer.

The multivariate analysis demonstrated that higher RES was significantly associated with worse OS in surgically-treated lung cancer, regardless of the tumor location and independent of smoking and COPD status. This finding was in line with previous studies where emphysema was quantified according to whole lung evaluation[313,504,507]. Zulueta and colleagues revealed that patients with mild, moderate, and marked emphysema had a respective HR of death from lung cancer of 1.4, 1.8 and 3.2 as compared with those patients who were free of emphysema[507]. Oelsner and colleagues demonstrated the association between quantitatively assessed emphysema and lung cancer mortality in which patients with worse emphysema had poorer outcomes[313]. These results indicated that RES had an impact on OS similar to that of generalized emphysema, and that a systemic effect of RES might underlie the prognostic association in this study cohort. Possible systemic mechanisms for the effect of regional emphysematous change on lung cancer survival could include the

tumor-promoting effect of neutrophilic inflammation[104,488,490], enhanced angiogenesis secondary to chronic inflammation[512], and up-regulation of matrix metalloproteinase (MMP) in emphysematous lungs[345,356]. Typically, emphysema was characterized by lung parenchymal destruction through the influx of neutrophils[513]. The neutrophilic inflammation in the context of lung cancer could inhibit cytotoxic lymphocytes to downregulate the immune response against cancers[104,490], and facilitate transendothelial migration of tumor cell to stimulate progression and metastasis[488]. There is evidence that the neutrophil count, or neutrophil to lymphocyte ratio, in the intratumoral microenvironment is inversely correlated with lung cancer outcomes[514]. In addition, chronic inflammation can activate angiogenesis and increase vascular permeability to provide support for the malignant cells, by which tumors are likely to behave as "wounds that do not heal"[512,515]. Up-regulation of MMP has been associated with lymphovascular tumor invasion and postoperative recurrence[356] and could potentially contribute to poorer outcomes with more severe RES.

Health-related QOL has been increasingly emphasized in lung cancer[106]. Previous studies found patient comorbidities, such as COPD, did not affect QOL for lung cancer patients[411,516]; however, the influence of emphysema is still uncertain. Our study showed that the overall QOL score did not differ significantly between RES whereas dyspnea scores were worse in patients with a severe RES in all groups. Dyspnea has been reported to constitute a major component of symptom burden in patients with lung cancer[499]. Balduyck and colleagues found a significant correlation between comorbidity index and postoperative dyspnea[517]. Our study further demonstrated that dyspnea symptoms were worse in patients with severe RES, regardless of tumor location and treatment modalities, indicating a need for proactive intervention to symptom of dyspnea when managing lung cancer patients with severe emphysema.

Fatigue is a common symptom of inoperable lung cancer[518]. Our study found that fatigue was associated with RES in non-surgical group. In comparison to patients with

mild RES, those with moderate/severe RES had a higher proportion of concomitant COPD and more severe airflow obstruction, which are negative predictors of QOL[498,519]. In addition, these patients tended to be current smokers, a known association with poor QOL[520]. Therefore, it is possible that the addition of targeted emphysema therapy and smoking cessation may improve patient's health-related outcome.

Lung function is the main limiting factor when planning surgery for early-stage lung cancer. It has been recognized that lobectomy may lead to an improvement in postoperative ventilation capacity in patients with moderate to severe pulmonary emphysema[392,521]. Our findings highlighted the predictive value of RES in postoperative recovery of pulmonary function. When tumor resection was performed in emphysematous region (group 1), patients with a higher RES had less marked decline in FEV_1% but greater reductions in RV, contributing to "volume reduction effect" on FEV_1/FVC (and subsequent increase in FEV1/FVC). This finding concurred with those of Ueda and colleagues[391], who reported an association between emphysematous lung tissue in resected lung and volume reduction effect on postoperative FEV_1/FVC. In contrast, when lung cancer occurred away from emphysematous region (group 2), no obvious volume reduction effect was noted after surgical resection. Therefore, the grading of regional emphysema by quantitative CT can help determine the optimal treatment of patients with early-stage NSCLC who have compromised lung function.

RES was significantly associated with postoperative pneumonia in both surgical groups. Prolonged air leak occurred more frequently in those patients with a severe RES, and a statistically significant difference was noted in group 1 (cancer in the emphysema region) for a severe RES compared with a mild or moderate RES. Possible mechanisms include poorer postoperative healing owing to more fragile, emphysematous tissue after[522].

The current study has several limitations. First, although our patient cohort was prospectively followed in the past decade, this study was retrospective and

observational in nature; thus, the potential bias could not be completely eliminated even with rigorous statistical analysis. Second, follow-up by lung function was not conducted routinely in the postoperative course; rather, the PFT data were passively collected upon availability in medical records; only one-fourth of patients had follow-up of lung function. Third, preoperative QOL was unavailable, which limits the ability of the study to assess the effects of therapy (and RES) on post-treatment change. Lastly, the relatively small number of early-stage patients who received non-surgical treatment in the present study limits interpretation of results for this group. Therefore, a larger-scale study is needed to confirm our results.

4.4 Chapter Summary

This study explored the prognostic significance of regional emphysema severity in a retrospective analysis and found that RES was an independent predictor of OS in early-stage NSCLC after surgery regardless of tumor location, and was associated with post-treatment QOL related to dyspnea and postoperative recovery of pulmonary function.

CHAPTER FIVE

IMPACT OF COMORBID COPD ON OVERALL SURVIVAL IN LUNG CANCER PATIENTS

Chronic obstructive pulmonary disease (COPD) and lung cancer are two leading causes of death in the world, which are projected to rank fourth and sixth by 2030, respectively[295]. Both are caused by cigarette smoking and there is an increasing evidence linking the two diseases through epidemiologic and genetic studies[246,420]. In clinical practice, the prevalence of COPD is estimated at 50% to 70% among patients diagnosed with lung cancer[296].

Recently, Durham and Adcock performed a review on the relationship between COPD and lung cancer, aiming to expand the understanding on mechanistic possibility of these two linked diseases[344]. Despite many studies from large national databases reporting the survival for primary lung cancer or COPD[111,134,523,524], the outcome of lung cancer coexisting with COPD, namely the prognostic significance of COPD in lung cancer is poorly understood. Lee and colleagues[405] reported that COPD did not worsen the prognosis for lung cancer after adjustment for baseline characteristics while Tammemagi and colleagues[525] found that the presence of COPD was an independent factor of a poor prognosis regardless of cancer stages. A recent meta-analysis discussed the impact of COPD and emphysema on lung cancer and indicated these as predictors of poor survival[406], but the study population included patients with emphysema without evidence of airway obstruction[128] and congestive heart failure[526], resulting in a high heterogeneity, thus some conclusions may be biased.

Since COPD is very prevalent in lung cancer patients and the conclusions from previous studies remain conflicting regarding the prognostic significance of COPD preceding lung cancer diagnosis, we aimed to systematically review the current available literature to verify and quantify the impact of COPD on survival of lung cancer patients.

5.1 Methods

5.1.1 Literature search strategy

A systematic search was performed using the PubMed database to identify articles mentioning the impact of COPD on overall survival (OS) in patients with lung cancer. Inclusion criteria were: (1) peer-reviewed and published original articles, (2) study populations involving 20 or more cases in each group (COPD group and non-COPD group), and (3) a hazard ratio (HR) and 95% confidence interval (CI) were stated, or could be calculated in the article. Publications were excluded if the study (i) was published in a book or in non-English, (ii) lacked accessibility of HR and 95%CI, or (iii) only described the severity of COPD and its relationship to lung cancer prognosis. If the enrolled patients came from the same institution and in the same period, the most proper study would be chosen according to the needs of stratified analysis.

A search strategy using the keywords "(chronic obstructive pulmonary disease) AND (lung cancer) AND survival" with the limitation of English language, human research and publication date through October 31, 2015 identified 672 articles (Figure 5.1). Of these, 629 were excluded on the basis of title or abstract and the full-text of 43 articles was reviewed. Three articles[366,527,528] were published from a single institution with the same study periods, so one study[527] was excluded and the other two articles[366,528] were divided into different analyses (i.e., stratified analyses by different cancer stages and treatment modalities) to avoid double counting the patients cohorts. Three additional studies[482,525,529] were identified from the reference in obtained articles. One published study from Mayo Clinic (Rochester, MN) was also added[523]. Finally, 16 studies were included in the meta-analysis.

5.1.2 Data extraction

The extracted data included (1) year of publication, (2) study design, (3) ethnic population, (4) number of patients, (5) diagnostic method of COPD, (6) histopathology and stage of lung cancer, (7) treatment for lung cancer, (8) OS in each group, and (9) HR and 95%CI in each study.

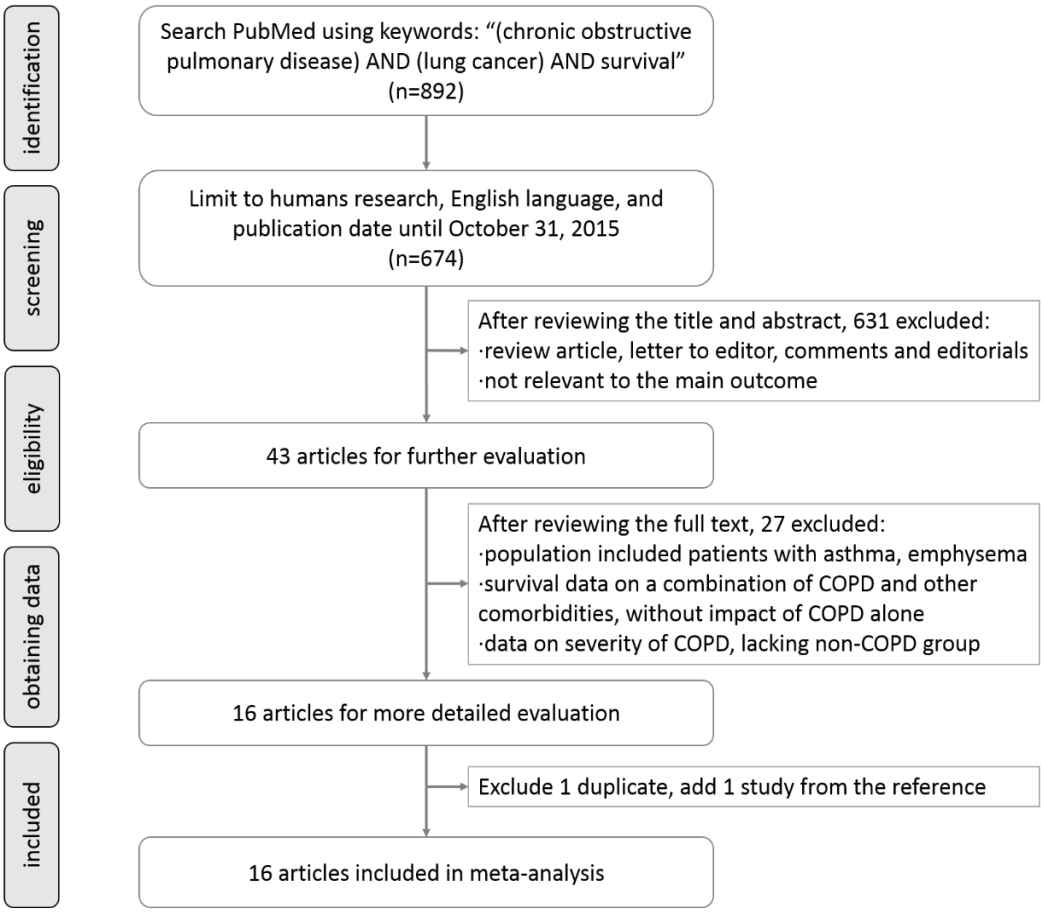


Figure 5.1: Literature selection procedures to identify relevant studies reporting the impact of COPD on overall survival in patients with lung cancer.

5.1.3 Statistical analysis

For each study, the log (HR) and its standard error were used as the outcome variables for data combination[530]. For the studies in which HR could not be achieved

directly, the Kaplan-Meier survival curves from original papers would be read by Engauge Digitize version 4.1 to extract data and to calculate the HR according to the methods introduced by Tierney and colleagues[530]. As shown in Figure 5.2, the HRs in 3 studies were calculated by data reading from Kaplan-Meier survival curves[366,403,531].

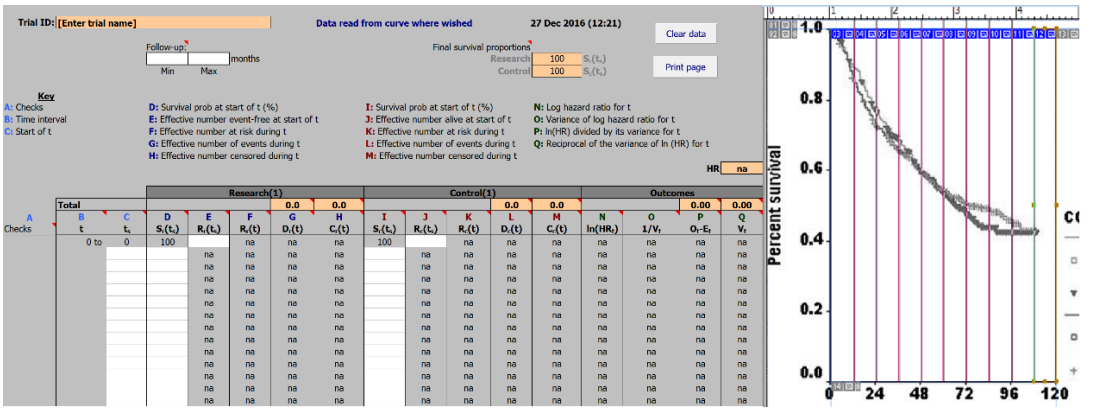


Figure 5.2: Data extraction from Kaplan-Meier survival curve using Engauge Digitize.

It is noted that there are obvious typographical errors in two papers which give the HR and 95%CI as 1.15[0.04, 2.23] and 0.74[0.83, 2.23], respectively[367,510]. Therefore, these HRs were regenerated as 1.15[0.93, 1.42] and 1.36[0.83, 2.23] by RevMan Calculator (Figure 5.3).

Figure 5.3: Correction of Hazard ratios in two studies using RevMan Calculator.

Meta-analysis was performed with RevMan version 5.1 using a random-effects model or a fixed-effect model according to the results of heterogeneity test. The heterogeneity among studies was assessed with the Cochrane Q test and I^2 statistics. The publication bias was detected by funnel plot visually, and analyzed by Egger's test quantitatively through Stata 12.0.

5.2 Results

The characteristics of the included studies are summarized in Table 5.1. Most studies were based on the retrospective analysis except for two (by Lopez-Encuentra[531] and Xie[523]), in which patients were enrolled prospectively. The data in four studies came from population-based studies or multicenter trials[403,529,531,532]. The size of the cohorts varied from 114 to 19,337, with a total number of 38,966 patients. COPD was mainly diagnosed by spirometry.

Table 5.1: General characteristics of included studies

Author, year of publication, study design	**Ethnicity**	**Diagnosis for COPD**	**Pathology of LC**	**Stage of LC**	**Treatment for LC**	**Total**
Xie[523] 2015, prospective	Caucasian	not mentioned	SCLC	extensive limited	all all	555 383
Iachina[529] 2015, retrospective, population-based	Caucasian	not mentioned	NSCLC	mixed	all	10378
Kuo[533] 2014, retrospective	Asian	spirometry	NSCLC	I	surgery	181
Zhai[402] 2014, retrospective	Caucasian	physician-diagnosed & self-report	NSCLC	IA-IIB	surgery	902
Izquierdo[404] 2014, retrospective	Caucasian	spirometry	NSCLC +SCLC	IIIB/IV	chemotherapy or TKI	324

Table 5.1: General characteristics of included studies

Author, year of publication, study design	Ethnicity	Diagnosis for COPD	Pathology of LC	Stage of LC	Treatment for LC	Total
Lee 2014[405], retrospective	Asian	spirometry	NSCLC	mixed	all	221
Sekine[366] 2013, retrospective	Asian	spirometry	NSCLC	mixed	surgery	1461
Mina[482] 2012, retrospective	Caucasian	spirometry	NSCLC +SCLC	mixed	all	114
Gullon[510] 2011, retrospective	Caucasian	spirometry	NSLCL	mixed	all	353
Kondo[534] 2011, retrospective	Asian	spirometry	NSCLC +SCLC	mixed	surgery	531
Kiri[403] 2010, retrospective, population-based	Caucasian	physician-diagnosed	NA.	NA.	NA.	19337
Birim[532] 2006, retrospective, multicenter	Caucasian	spirometry	NSCLC	mixed	all	776
Lopez-Encuentra[531] 2005, prospective, multicenter	Caucasian	spirometry	NSCLC	IA/IB	surgery	2051
Tammemagi[525] 2003, retrospective	Caucasian	not mentioned	NSCLC +SCLC	mixed I/II III//IV	all	1155 304 851
Sekine[367] 2002, retrospective	Caucasian	spirometry	NSCLC	mixed	surgery	244
Sekine[528] 2007, retrospective*	Asian	spirometry	NSCLC	IA	surgery	442

* only used in stage-specific subgroup analysis;

COPD: chronic obstructive pulmonary disease; LC: lung cancer; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; OS: overall survival; TKI: tyrosine kinase inhibitors; NA: not available.

5.2.1 General Impact in all patients

A meta-analysis for all 15 publications reporting the impact of COPD on OS of lung cancer was shown in Figure 5.4a. The statistical heterogeneity was non-significant (p=0.11, I^2=32%), and thus a fixed-effect model was used. The result suggested that COPD was an adverse prognostic factor in lung cancer (HR, 1.22; 95%CI, 1.18-1.27). The funnel plot displays a symmetric distribution (Figure 5.9a), and no sign of publication bias was proved by Egger's test (p=0.760).

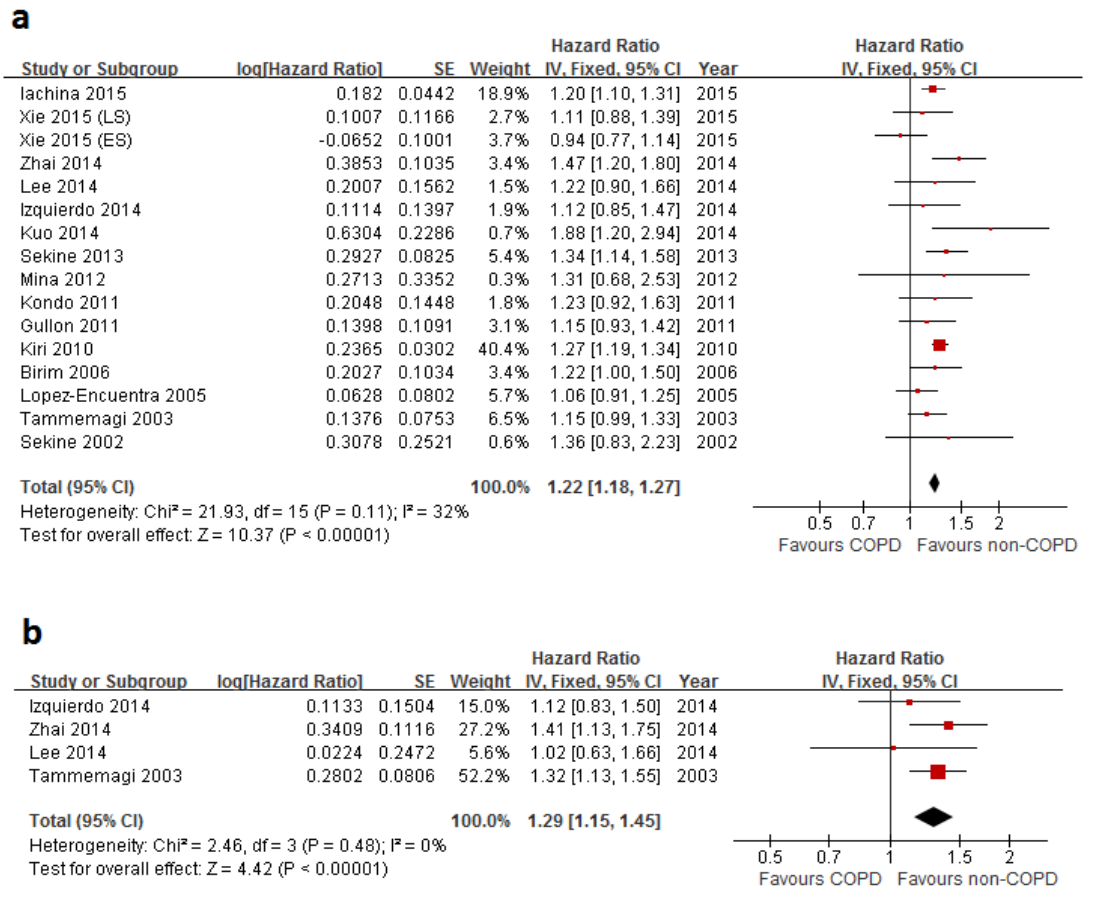


Figure 5.4: Forest plots of HR for the impact of COPD on survival of lung cancer: a) HRs gained from univariate analysis, b) adjusted HRs gained from multivariate analysis in original studies.

After adjustment for important covariates such as age, gender, smoking status, performance status and stage of lung cancer, the result (Figure 5.4b), on the basis of

adjusted HRs in 4 available studies[402,404,405,525], suggested that COPD was an independent deleterious factor (HR, 1.29; 95%CI, 1.15-1.45). No significant heterogeneity was found (p=0.48, I^2=0%). The funnel plot (Figure 5.9b) shows symmetry indicating no obvious publication bias, as confirmed by Egger's test (p=0.062).

5.2.2 Stratified analysis based on ethnic populations

When stratified by different ethnicities, the association remained significant in both Asians (HR, 1.33; 95%CI, 1.18-1.51) and Caucasians (HR, 1.21; 95%CI, 1.16-1.26), respectively (Figure 5.5). There was no significant heterogeneity detected in any subgroups; with respective Cochran test and I^2 statistics for Asian and Caucasian population being p=0.41, I^2=0% and p=0.11, I^2=35%.

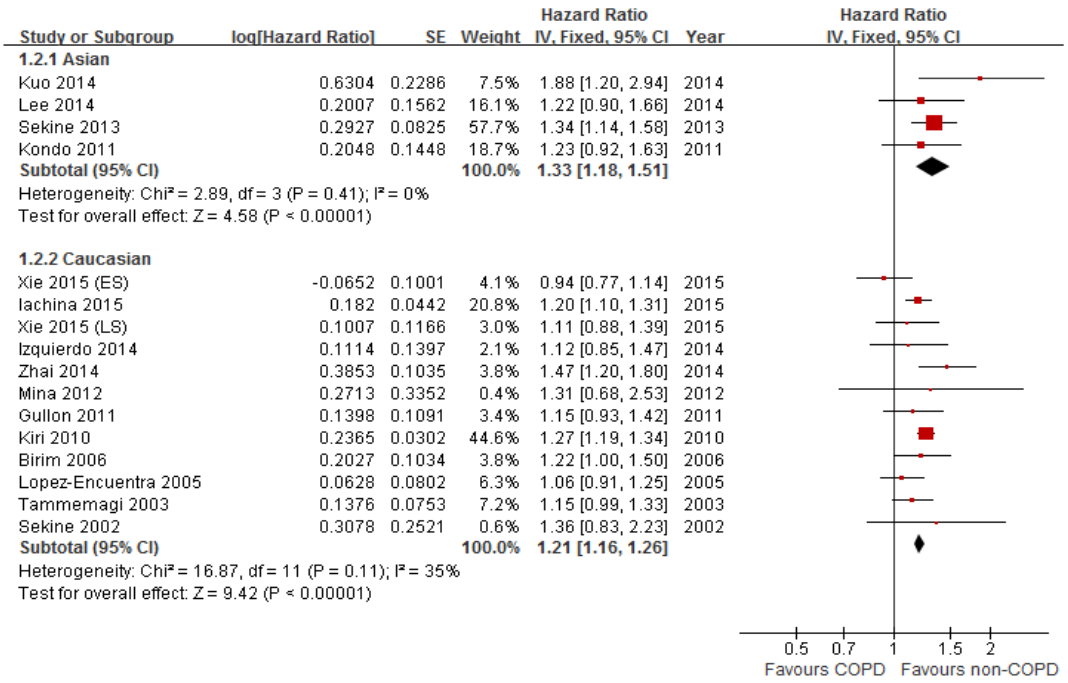


Figure 5.5: Forest plots of HR for the impact of COPD on survival of lung cancer in different ethnic groups.

5.2.3 Stratified analysis according to cancer types

Histopathologic types of lung cancer were non-small cell lung cancer (NSCLC) in nine studies, small cell lung cancer (SCLC) in one study, and mixed types (NSCLC+SCLC) in four studies (Figure 5.6). A stratified analysis showed that the difference in OS between patients with and without COPD was significant in NSCLC (HR, 1.23; 95%CI, 1.16-1.30), less significant in mixed types (HR, 1.16; 95%CI, 1.03-1.30), but not significant in SCLC (HR, 1.01; 95%CI, 0.87-1.17). No obvious heterogeneity in each group (p=0.17, I^2=31%; p=0.94, I^2=0%; p=0.28, I^2=14%) or publication bias (p=0.462) was detected.

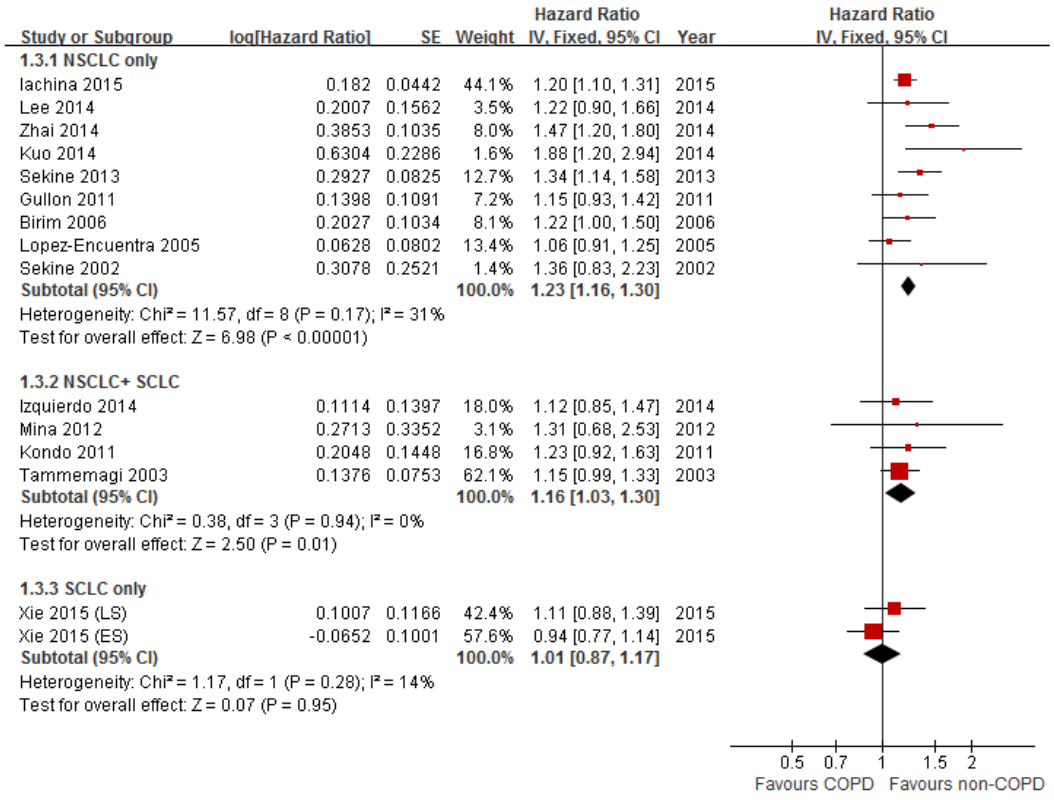


Figure 5.6: Forest plots of HR for the impact of COPD on survival of lung cancer in different histopathologic types.

5.2.4 Stratified analysis according to cancer stages

Seven studies reported the impact of COPD in stage-specific lung cancer including six publications studying early stage (stage I-II or limited stage) and three publications studying late stage (stage III-IV or extensive stage) (Figure 5.7). A stratified analysis showed that COPD had a significantly negative impact on early stage lung cancer (HR, 1.35; 95%CI, 1.12-1.63) but not on late stage lung cancer (HR, 1.08; 95%CI, 0.92-1.27). Because the statistical heterogeneity was moderate in the early stage subgroup (p=0.03, I^2=62%), a random-effects model was used. No significant publication bias was found by either funnel plot (Figure 5.9c) or Egger's test (p=0.058).

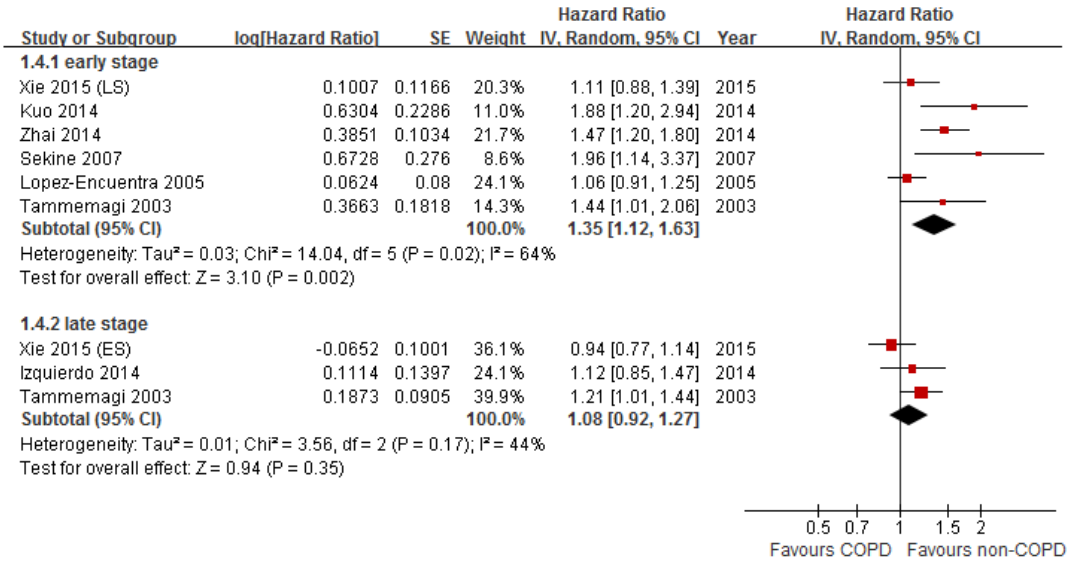


Figure 5.7: Forest plots of HR for the impact of COPD on survival of lung cancer in different cancer stages.

5.2.5 Stratified analysis according to treatment modalities

Only one study[404] focused on patients receiving non-surgical treatment (chemotherapy and/or tyrosine kinase inhibitors) and the result suggested that COPD has no impact on the mortality in this population (HR, 1.12; 95%CI, 0.85-1.47). In

patients receiving surgical treatment (Figure 5.8), six studies were included and a pooled analysis showed a significant association between the presence of COPD and worse OS (HR, 1.31; 95%CI, 1.13-1.51). The statistical heterogeneity was mild (p=0.07, I^2=52%), so that a random-effects model was used. The funnel plot shows symmetry (Figure 5.9d) and no publication bias was detected (p=0.316).

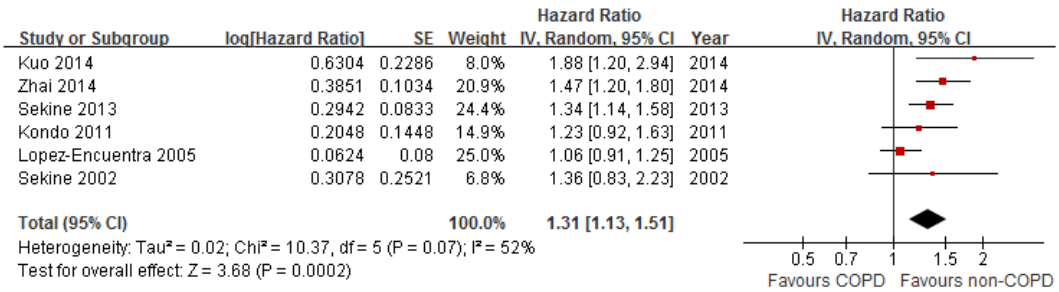


Figure 5.8: Forest plots of HR for the impact of COPD on survival of lung cancer in surgically treated lung cancer.

5.3 Discussion

This meta-analysis based on 16 studies which examined the association between the presence of COPD and the prognosis of lung cancer has verified that COPD had a significant deleterious impact on lung cancer survival regardless of the ethnic groups studied. In addition, the impact of COPD appeared to be more pronounced in NSCLC, early stage, and surgically-treated patients.

Recently, many studies were keen on the relationship between COPD and the risk of lung cancer[246,296,347]; however, the prognostic impact of COPD on lung cancer is not clearly defined. To our knowledge, this is the first meta-analysis to quantify its impact based on a strict screening for patients with COPD. In previous studies, COPD was shown to correlate with higher rates of tumor recurrence and metastasis[528,533], with underlying mechanism by which COPD affects the prognosis of lung cancer remaining

elusive. Some studies indicated that a host environment with chronic inflammation could contribute to the poor prognosis[535,536]. Besides, genetic and epigenetic pathway in, for example, SPARC, p16 and smoking-related CXCL14 gene may also modulate the prognosis[363,537].

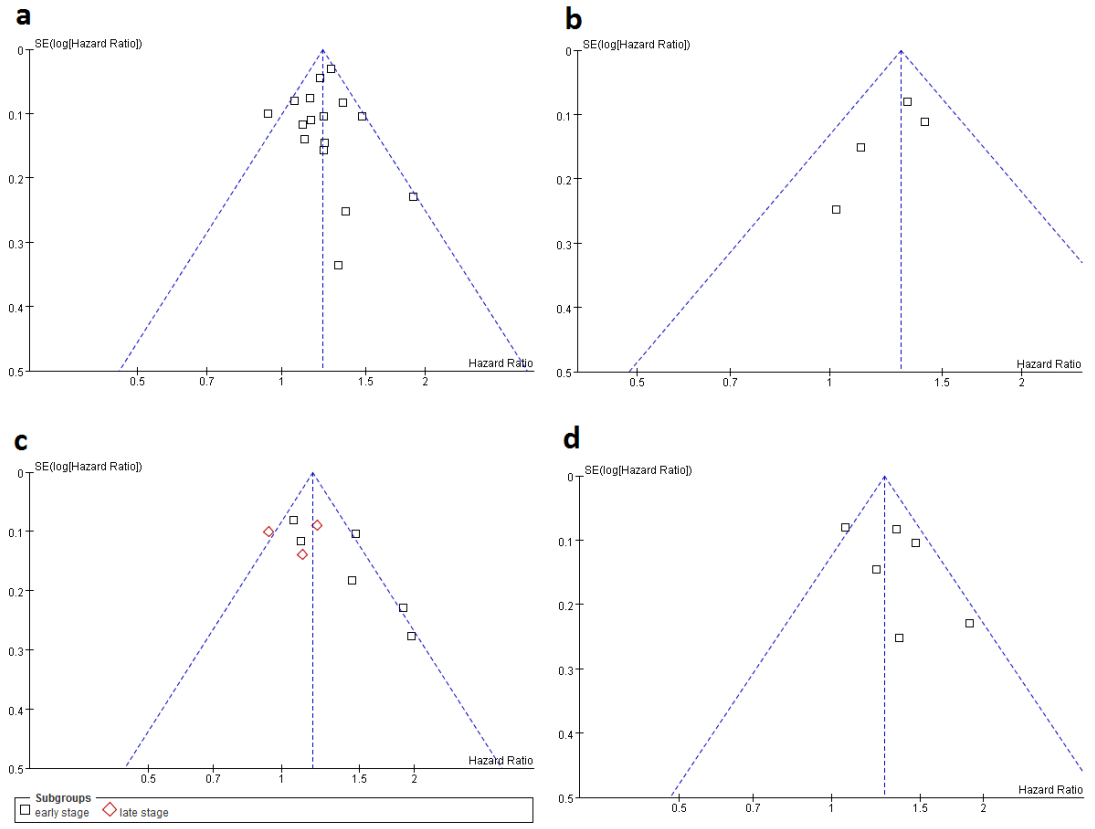


Figure 5.9: Funnel plots of meta-analysis. (a) impact of COPD on OS in lung cancer patients; (b) impact of COPD on OS on the basis of adjusted HRs; (c) impact of COPD on OS in stage-specific lung cancer patients; (d) impact of COPD on OS in surgically treated lung cancer patients.

COPD is characterized by two components: airflow obstruction (bronchitis) and peripheral airspace disease (emphysema), and chronic inflammation is involved in both of their pathogenesis[134,167]. One common feature of this chronic inflammation is the influx of neutrophils[490] while the neutrophilic inflammation in the context of lung cancer may act as a dual-edged sword[538]. On one hand, it can suppress tumor progression by means of direct tumor cytotoxicity[539]. On the other hand, it may possess a tumor-promoting effect not only to survive cancer cells by suppressing the

action of cytotoxic lymphocytes[490] , but also to promote tumor metastasis by facilitating tumor cell transendothelial migration[488]. As a result, many studies indicated that the neutrophil count or neutrophil to lymphocyte ratio in the tumor and/or in the peripheral blood inversely correlated with the outcome in various types of solid cancers, including SCLC[523] and NSCLC[490,514].

Another mechanistic explanation proposed by Dvorak and colleagues is that chronic inflammation can activate angiogenesis and increase vascular permeability[515], which provides support for the malignant cells, by which tumors are likely to behave as "wounds that do not heal".[512] Additionally, in some cases, inflammation could diminish the beneficial effects of therapy[540]. Clinically, Berry and colleagues has disclosed an apparent decrement in survival for patients with lower pulmonary function[541]. Therefore, considering the results documented previously and presented in our study, COPD did negatively impact the long-term outcome in lung cancer, and this disadvantage was also observed after the adjustment for important prognostic factors (e.g., smoking status, performance status, and stage of disease). Further studies including genomic and epigenetic analysis to explore and verify this prognostic link are still warranted, which could serve as a novel biologic target for both prevention and treatment of lung cancer with COPD.

In this meta-analysis, examinations for pooled HR were performed among all ethnic, pathological, and staging subgroups. The presence of COPD had a negative influence in both examined ethnicities (Asian and Caucasian). Histopathologically, the association of COPD with NSCLC survival seemed more pronounced than that with SCLC, because the pooled HR was significant in NSCLC but not significant in SCLC. We hypothesize that this subgroup-specific association can be partly explained by a highly aggressive nature and a rapid disease progression of SCLC, which could minimize or overwhelm any potential influence of patient's comorbidities like COPD on survival[542].

Although there likely be an interaction between stage of disease and choice of

treatment for lung cancer, we are unable to conduct a multivariate model for the meta-analysis because of the inconsistent data provided in the published studies. When analyzing stage-specific subgroup separately, the pooled HR was significant in early stage but not significant in late stage lung cancer. Although only three studies were eligible for analysis in the late stage subgroup, the HR in each study was merely marginally significant or even not significant.

With regard to treatment modalities, one study by Izquierdo and colleagues demonstrated no influence of COPD on OS of lung cancer in patients receiving non-surgical treatment[404] whereas our meta-analysis revealed a worse survival in surgically-treated patients with COPD. Owing to the fact that surgical treatment is commonly associated with diseases in the early stage, it is reasonable to infer that the influence of COPD is more evident in patients at an early stage and/or receiving surgical treatment. However, this result did not mean that patients with COPD were unfit for surgery, because lung resection for tumor sometimes had volume reduction benefit, contributing to improved quality of life[381]. The findings of this investigation highlight the association of COPD and lung cancer prognosis, disclosing the inhomogeneous magnitude of COPD in different phases of lung cancer, thus aiding the decision-making process when clinicians are selecting best possible strategies for the management and long-term monitoring in this particular population, especially in the field of multidisciplinary care for inflammation control and pulmonary rehabilitation because both may be beneficial to lung cancer outcome.

There were several limitations in the current study. First, the majority of the enrolled studies were retrospective and the numbers of studies in the subgroups were relatively small, which might be subject to some biases, such as selection bias. Second, due to the lack of accessible data, we were unable to perform a stratified analysis by severity of COPD since the result by Sekine and colleagues suggested that the severity of COPD was related to lung cancer prognosis[366]. Third, two HRs in this meta-analysis

were obtained from the data in 2-year and 3-year follow-ups[403,482], which may be not as accurate as the HRs calculated from 5-year follow-up information. Future studies should supplement the impact of COPD on survival of SCLC and in patients with other non-surgical treatment, and investigate the mechanisms underlying the association of COPD with lung cancer prognosis.

5.4 Chapter Summary

our meta-analysis not only has confirmed that COPD is an independent prognostic factor of lung cancer survival, but also demonstrated that the deleterious impact tends to be more pronounced in patients with non-small cell lung cancer, at an early-stage, and on those who received surgical treatment. Further mechanistic investigations for this relationship and potential clinical interventions are warranted.

CHAPTER SIX

GENETIC VARIATIONS AND SURVIVAL IN LUNG CANCER SUBGROUPING BY COPD

Lung cancer is a rapidly fatal disease with poor long-term prognosis; the average 5-year overall survival rate is estimated to be below 20% across all stages[543]. Non-small cell lung cancer (NSCLC) constitutes more than 80% of all lung cancers[17]. Despite recent progress in lung cancer treatment, such as targeted therapy and immunotherapy[544-546], lung cancer remains the leading cause of cancer specific morality for both men and women in the world[32]. Thus, considerable efforts are dedicated to risk stratification and optimal management of lung cancer.

It is increasingly clear that inherited genetic factors play a central role in the clinical outcomes of lung cancer patients. Several genome-wide association (GWA) studies and candidate gene studies have identified a variety of putative polymorphic biomarkers related to lung cancer prognosis[547-551]. Hence, independent replication of these findings is needed to aid better understanding and provide irrefutable and accurately quantified evidence of these identified genetic associations.

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation, is the third leading cause of death worldwide[130,134]. Approximately 40-60% patients with lung cancer have concomitant COPD[402,404], and lung cancer arising in COPD has a unique profile of disease manifestation and clinical outcomes[481]. Nevertheless, in many of the previous studies examining associations between genetic variants and lung cancer survival, COPD status has not been taken fully into account. Young and colleagues argued that some genetic loci implicated in COPD might be mistakenly attributed to lung cancer, due to the failure to identify the coexisting COPD[421]. In addition, there is accumulating evidence suggesting the genetic associations overlap to some degree between lung cancer and COPD (see Chapter 2). Hence, integrated research is required in the association analyses including genetic variations, COPD, and lung cancer survival[552,553].

Therefore, this study aimed to identify specific genetic markers associated with lung cancer survival, and to examine whether the associations were influenced by

COPD status.

6.1 Methods

6.1.1 Patient cohort

The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board. Detailed procedures of patient enrollment, data collection, and follow-up can be found in the Appendix. Patients with pathologically confirmed NSCLC between 1997 and 2013 were included in this study. Informed consent was obtained from all participants.

The diagnosis of COPD was determined by examination of the patient's medical record and/or documented irreversible airflow limitation, i.e., post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of less than 70%[134]. In the current study, tumor grade was classified into well-, moderately-, and poorly-differentiated[100]. Treatment modalities included surgery alone, surgery plus adjuvant therapy (chemotherapy and/or radiation), chemoradiation (concurrent or sequential), and chemotherapy or radiotherapy only or other supportive care.

6.1.2 SNP selection and genotyping

We selected 384 SNPs from 332 genes following a review of the lung cancer literature and based on out previous unpublished GWA studies (Appendix Table 1)[447,554,555]. Genomic DNA was extracted from peripheral blood using the QIAmp DNA extraction kit (Qiagen) and genotyped in the Mayo Clinic Genomics Shared Resource using a custom-designed Illumina GoldenGate panel.

Quality control was implemented in multiple steps, as described previously[554]. In brief, SNPs were removed from subsequent analysis if they had call rates less than 95%, or Hardy-Weinberg equilibrium (HWE) p values less than 10^{-4}, or minor allele frequencies (MAF) less than 0.01 in this study population. In addition, samples with call rates of less than 95% were excluded at the same time. As such, 1 SNP failed genotyping, 16 SNPs had missing call rates more than 5%, 4 SNPs had MAF less than 1%, and 14 SNPs deviated from HWE, resulting in 349 SNPs being included in the further analyses (Appendix Table 2).

6.1.3 Statistical analysis

Data was compared across groups using the chi-square (x^2) test for categorical variables, and the unpaired t-test for continuous variables. According to the COPD status, patients were categorized into 2 groups: lung cancer with COPD (LC+COPD), and lung cancer without COPD (LC only). In each group, Cox proportional hazards models were performed using backward selection to identify potential confounders: patient's age, sex, race, smoking status, histological type, tumor grade, pathological stage, and treatment modality. The significant variables ($p<0.05$) were retained as covariates in the subsequent genetic association tests.

For each SNP that passed quality control thresholds, a Cox regression model was used to assess the associations between SNP genotypes and overall survival while adjusting for covariates. Hazard ratio (HR) and 95% confidence interval (CI) were estimated for the rare homozygous and heterozygous genotypes versus the common homozygote genotype. The best genetic model was determined by comparing the hazard ratios of three models: dominant (major allele homozygotes versus minor allele carrying genotypes), recessive (major allele carrying genotypes versus rare homozygotes), and additive (*P* for trend). If the rare homozygous genotype was

observed at a frequency <5% of total, only the dominant model was considered. To correct for multiple comparisons, q values (a false discovery rate-adjusted p value) were computed for each SNP, and a false discovery rate (FDR) of 20% was accepted[556].

Survival curves were generated by the Kaplan-Meier method to assess the differences in survival time by genotype from each individual SNP. Linkage disequilibrium measures (D') were used to detect association between identified SNPs. The likelihood ratio test was used to compare the difference in HR and 95%CI of each SNP between LC+COPD model and the LC only model by comparing the model with and without the COPD*SNP interaction term. All analyses were performed in SAS, version 9.3 (SAS Institute) or R software (version 3.3.1)

6.2 Results

6.2.1 Patient clinical features

A total of 1,694 patients were identified in this study (Table 6.1). The mean age of all patients was 65.5±10.9 years, with slightly more women (51.9%) than men (48.1%). The diagnosis of COPD was identified in 767 (45.3%) patients. Compared to those without COPD, COPD was noted more frequently in male patients (53.1% vs. 43.9%, $p=1.7\times10^{-4}$) and smokers (78.4% vs. 45.1%, $p=7.7\times10^{-43}$). Squamous cell carcinoma represented 19.0% of the patient population, with a significantly higher rate in the LC+COPD group (26.5% vs. 12.8%, $p=6.4\times10^{-12}$). Due to a higher proportion of early stage NSCLC (stage I and II) in cases with COPD, treatment with surgery alone was also noted more frequently in the LC+COPD group than that in the LC only group.

Table 6.1: Patient demographic and clinical characteristics

	LC+COPD n=767 (45.3%)	LC only n=927 (54.7%)	total n=1,694	p
age (years)	67.8±9.6	63.7±11.5	65.5±10.9	**5.5E-15**
sex				**1.7E-04**
male	407 (53.1%)	407 (43.9%)	814 (48.1%)	
female	360 (46.9%)	520 (56.1%)	880 (51.9%)	
race				1.4E-01
white	714 (93.1%)	845 (91.2%)	1559 (92.0%)	
non-white	53 (6.9%)	82 (8.8%)	135 (8.0%)	
smoking status				**7.7E-43**
never	166 (21.6%)	509 (54.9%)	675 (39.8%)	
former	381 (49.7%)	270 (29.1%)	651 (38.5%)	
current	220 (28.7%)	148 (15.9%)	368 (21.7%)	
cell type				**6.4E-12**
adenocarcinoma	454 (59.2%)	667 (72.0%)	1121 (66.2%)	
squamous cell	203 (26.5%)	119 (12.8%)	322 (19.0%)	
other NSCLC	110 (14.3%)	141 (15.2%)	251 (14.8%)	
tumor grade				**2.1E-03**
well differentiated	187 (24.4%)	232 (25.0%)	419 (24.7%)	
moderately differentiated	361 (47.1%)	365 (39.4%)	726 (42.9%)	
poorly differentiated	219 (28.6%)	330 (35.6%)	549 (32.4%)	
pathological stage				**9.2E-23**
I	370 (48.2%)	300 (32.4%)	670 (39.6%)	
II	118 (15.4%)	90 (9.7%)	208 (12.3%)	
III	165 (21.5%)	209 (22.5%)	374 (22.1%)	
IV	114 (14.9%)	328 (35.3%)	442 (26.1%)	
therapy				**6.7E-21**
surgery alone	458 (59.7%)	347 (37.4%)	805 (47.6%)	
surgery + adjuvant therapy	111 (14.5%)	150 (16.2%)	261 (15.4%)	
chemo-/radio-/other only	116 (15.1%)	292 (31.5%)	408 (24.1%)	
chemoradiation	82 (10.7%)	138 (14.9%)	220 (13.0%)	

Bold values indicate P values with statistically significant difference ($p<0.05$).

6.2.2 Baseline survival model

The overall median survival and 5-year survival rate for the entire cohort were 4.5 years and 47.3%, respectively. In the analysis of patient characteristics, 6 variables were simultaneously associated with overall survival: age, sex, race, tumor grade, pathological stage, and treatment modality (Appendix Table 3.1).

In the LC+COPD cohort, the median survival and 5-year survival rate were 5.6 years and 53.0%, respectively. The Cox proportional hazards model indicated age, sex, tumor grade, pathological stage, and treatment modality were significantly associated with overall survival (Appendix Table 3.2). In the LC only cohort, the average 5-year survival rate was lower at 42.5%, with a median survival time of 3.7 years, most likely due to the proportion of patients whose lung cancers were diagnosed at an advanced stage. Age, tumor grade, pathological stage, and treatment modality were shown to be related to survival in this group (Appendix Table 3.3). Therefore, these identified variables were considered to be potential confounders and were adjusted in the subsequent SNP analyses.

6.2.3 Associations of individual SNPs with survival

The analysis of SNPs and survival in the whole cohort identified 28 SNPs with $p<0.05$ in the multivariate Cox model (Appendix Table 4.1), of which only 1 SNP (rs10218481) passed the FDR<20% assessment ($p=4.46\times10^{-4}$, q=0.16). Each additional variant allele contributed to a 14% reduction in risk of death (HR, 0.86; 95%CI, 0.89-0.94).

In the stratified analysis of the LC+COPD cohort, 24 SNPs were associated with lung cancer survival ($p<0.05$, Appendix Table 4.2), with one SNP (rs74798757) with q value less than 0.20 ($p=1.56\times10^{-4}$, q=0.05). Patients carrying the rare allele had a

significantly poorer overall survival (HR, 1.68; 95%CI, 1.29-2.20).

In the LC only cohort, there were 32 SNPs related to lung cancer survival (Appendix Table 4.3), and 5 SNPs remained significant after FDR correction (Table 2). Consistent with the total cohort, the rs10218481 polymorphism showed a similar protective effect on overall survival (HR, 0.81; 95%CI, 0.73-0.91; $p=4.19\times10^{-4}$, q=0.12). In the dominant model, improved survival was observed in patients with the minor allele of rs17090907 (HR, 0.71; 95%CI, 0.58-0.87; $p=9.18\times10^{-4}$, q=0.12). In addition, the variant alleles of the two *GPC5* SNPs, rs1409600 (HR, 0.73; 95%CI; 0.61-0.89, $p=1.38\times10^{-3}$, q=0.12) and rs163933 (HR, 0.73; 95%CI; 0.60-0.89, $p=1.59\times10^{-3}$, q=0.12) were associated with decreased death risk. In contrast, the variant allele of rs8192627 displayed an association with worse survival (HR, 1.41; 95%CI, 1.14-1.74; $p=1.79\times10^{-3}$, q=0.12). The Survival curves for the 6 identified SNPs are shown in Appendix Figure 1.

Table 6.2: SNPs associated with lung cancer survival

SNP	gene	chr	best model	total		
				HR (95%CI)	p	q
rs10218481	*NR5A2*[*]	1	Additive	0.86 (0.79, 0.94)	4.46E-04	**0.16**
rs74798757	*HAAO*[*]	2	Dominant	1.28 (1.04, 1.57)	2.06E-02	0.46
rs17090907	*CASP7*	10	Dominant	0.85 (0.74, 0.99)	3.21E-02	0.48
rs1409600	*GPC5*	13	Dominant	0.86 (0.75, 0.98)	2.81E-02	0.46
rs163933	*GPC5*	13	Dominant	0.86 (0.75, 0.99)	3.86E-02	0.50
rs8192627	*TAAR8*	6	Dominant	1.22 (1.04, 1.42)	1.38E-02	0.46

SNP	LC+COPD			LC only		
	HR (95%CI)	p	q	HR (95%CI)	p	q
rs10218481	0.92 (0.82, 1.05)	2.09E-01	0.85	0.81 (0.73, 0.91)	4.19E-04	**0.12**
rs74798757	1.68 (1.29, 2.20)	1.56E-04	**0.05**	0.98 (0.70, 1.36)	8.99E-01	0.97
rs17090907	1.10 (0.89, 1.35)	3.71E-01	0.88	0.71 (0.58, 0.87)	9.18E-04	**0.12**
rs1409600	1.02 (0.83, 1.24)	8.71E-01	0.98	0.73 (0.61, 0.89)	1.38E-03	**0.12**
rs163933	1.03 (0.84, 1.27)	7.56E-01	0.96	0.73 (0.60, 0.89)	1.59E-03	**0.12**
rs8192627	1.07 (0.84, 1.35)	5.94E-01	0.96	1.41 (1.14, 1.74)	1.79E-03	**0.12**

[*]nearest gene; underlined numbers denote significant association at q<0.20;

HR: hazard ratio; CI: confidence interval.

Likelihood ratio tests revealed that rs74798757 ($p=9.60\times10^{-3}$), rs17090907 ($p=2.17\times10^{-3}$), rs1409600 ($p=2.51\times10^{-2}$), and rs163933 ($p=2.36\times10^{-2}$) had significant interactions with COPD status, indicating that the effects of these SNPs on survival differ between lung cancer with COPD and lung cancer without COPD.

6.2.4 Cumulative risk assessment

Pairwise linkage disequilibrium measurements indicated that rs1409600 was in strong linkage disequilibrium with rs163933 (D'=0.92), representing a potential single association signal in the *GPC5* gene. Therefore, the more significant SNP, rs1409600, was selected in subsequent joint analysis. In the LC only cohort, when the 4 significant SNPs (rs10218481, rs17090907, rs1409600, and rs8192627) were included in a single multivariate Cox model, the significance remained for all of the 4 SNPs (Table 6.3).

Table 6.3: Multivariate Cox analysis of significant SNPs in LC only cohort

	best model	HR (95%CI)*	p
rs10218481	additive	0.83 (0.74, 0.93)	1.07E-03
rs17090907	dominant	0.72 (0.59, 0.88)	1.40E-03
rs1409600	dominant	0.74 (0.61, 0.89)	1.69E-03
rs8192627	dominant	1.37 (1.11, 1.70)	3.80E-03

*adjusted for age, tumor grade, pathological stage, and therapy. HR: hazard ratio; CI: confidence interval.

In the analysis of cumulative effect, each of the SNPs were assigned point scores corresponding to the direction of their HR estimates in the multivariate Cox model (Table 6.3). An unfavorable genotype was given 1 point. For SNP rs10218481 the effect was consistent with an additive model, and the risk score was the number of risk alleles carried by each patient. Thus, the total score was the sum of component scores from each of the SNPs. Due to the small number of patients with a total score of 0 (n=8), these were combined with those having a total score of 1, to constitute the reference

group. Patients with a higher score had a worse survival (Table 6.4); each increment of 1 unit in risk score indicated a 29% greater risk of death. When the total risk score was further divided into low-risk category (scores between 0 and 2 points) and high-risk category (scores between 3 and 5 points), the latter conferred a 1.73-fold increased risk of death (95%CI, 1.46-2.06) in comparison to the low-risk category.

Table 6.4: Genotypes score-based prediction model for survival in LC only cohort

genotype risk score	No. of patients N=927	dead N=641	multivariate HR (95%CI)*	p
0-1	67 (7.2%)	38 (56.7%)	reference	
2	235 (25.4%)	150 (63.8%)	1.31 (0.92, 1.88)	1.35E-01
3	361 (38.9%)	251 (69.5%)	2.04 (1.45, 2.88)	4.81E-05
4	228 (24.6%)	173 (75.9%)	2.24 (1.57, 3.20)	8.35E-06
5	36 (3.9%)	29 (80.5%)	2.53 (1.56, 4.12)	1.79E-04
per score (trend test)			1.29 (1.19, 1.39)	2.98E-10

*adjusted for age, tumor grade, pathological stage, and therapy. HR: hazard ratio; CI: confidence interval.

The significance of the scoring system was also confirmed in Kaplan-Meier analysis ($p=5.25\times10^{-5}$, Figure 6.1). However, no correlation was found between the risk score system and survival in the LC+COPD cohort (p=0.94).

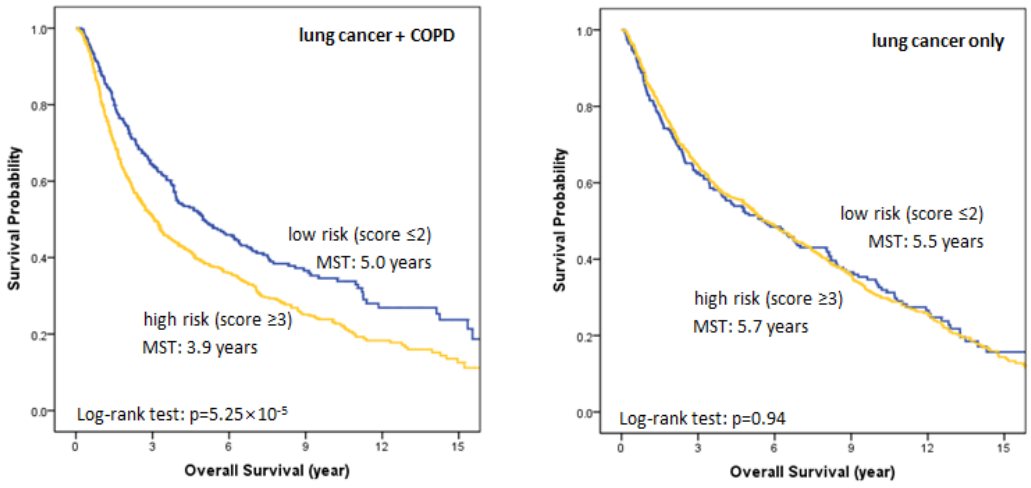


Figure 6.1: Kaplan-Meier estimates of overall survival grouped by the genetic risk score in the lung cancer only cohort.

6.3 Discussion

In this study, we have examined previously reported lung cancer risk SNPs in relation to survival, and investigated the role of COPD status in the association between genetic variants and lung cancer prognosis. Our results demonstrated that SNP rs74798757 was significantly associated with survival from lung cancer when COPD was also present, whereas SNP rs10218481, *CASP7*:rs17090907, *GPC5*:rs1409600, *GPC5*:rs163933, and *TAAR8*:rs8192627 showed predictive effects on overall survival in lung cancer patients who were free of COPD. To the best of our knowledge, this is the first evidence suggesting a difference in prognostic genetic effects between lung cancer arising in COPD and non-COPD.

Lung cancer is often concomitant with COPD, and they are closely linked above and beyond their associations with smoking[415]. Numerous studies have demonstrated that the presence of COPD is an important risk factor for both lung cancer development and its ultimate prognosis[296,306,407,481]. Additionally, lung cancer developing on a background of COPD has a distinct genetic profile from that without COPD[421,557]. Therefore, it is necessary to study the genetic factors influencing lung cancer survival in the presence or absence of COPD separately.

For individual SNP analysis in the LC only cohort, rs1409600 and rs163933, located in the *GPC5* gene, showed strong associations with survival. *GPC5* is a member of glypican gene family, and spans a large genomic region of 1.47 Mb at 13q31.3[558]. Evidence to date suggests that *GPC5* is involved in the signaling pathways of Wnt, hedgehog (Hh), and fibroblast growth factors (FGF)[559,560]. It has been reported that *GPC5* polymorphisms are associated with lung cancer susceptibility in never smokers[447,561], with downregulation of *GPC5* levels being detected in lung adenocarcinoma tissue[447,562]. Consistent with this finding, overexpression of *GPC5* has been shown to suppress proliferation, migration and invasion activities of lung cancer

cells in vitro[562,563]. Previous studies have found that level of *GPC5* expression might have an impact on lung cancer prognosis, although the results are still conflicting[563,564]. Our study demonstrated that polymorphisms in *GPC5* (rs1409600 and rs163933) were significantly associated with lung cancer survival; patients carrying the variant allele of the SNPs had a 27% reduced risk of death compared to those of the wildtype homozygous genotype. These two SNPs are in close linkage disequilibrium (D'=0.92), and both are intronic and not in any obvious functional elements. Therefore, they are most likely linked with other functional loci that regulate the expression of *GPC5*. Nevertheless, it is of note that neither of the two SNPs was implicated in lung cancer survival with concomitant COPD (rs1409600: HR=1.02; p=0.87; rs163933: HR=1.03; p=0.76), suggesting a prognostic role for *GPC5* in lung cancer only. The functional basis for the association of this gene with lung cancer survival dependent upon COPD status requires further study.

An intronic variant (rs17090907) located it the *CASP7* gene was also found to relate to lung cancer survival. Caspases (CASPs), members of the cysteine-aspartic acid protease family, serve as the central components of the apoptotic response, and *CASP7* plays a crucial part in the execution of the final cell death program[565]. Many studies have shown that polymorphisms in *CASP7* gene are associated with the risk of lung cancer[566,567]. It has also been reported that the *CASP7* rs2227310 polymorphism can be a potentially prognostic marker for early-stage NSLCL after surgical resection[568], and genetic variants at rs4353229 and rs12415607 may affect survival in lung cancer treated with platinum-based chemotherapy[569]. We used LDlink to compute the LD coefficients between rs17090907 and the other 3 reported SNPs[570]. The results of the LDlink analysis showed that the r^2 ranged from 0.034 to 0.039, suggesting that these SNPs are not in linkage disequilibrium (Appendix Figure 2). Nevertheless, through eQTL analysis on the GETx Portal (https://gtexportal.org/home/), the rs17090907 genotypes were significantly correlated with the expression level of the *CASP7* gene in normal lung tissue ($p=1.2\times10^{-9}$, Figure 6.2). Hence, the *CASP7* rs17090907 can be a promising

prognostic factor of survival in lung cancer; future biological studies should elucidate this relationship in more detail.

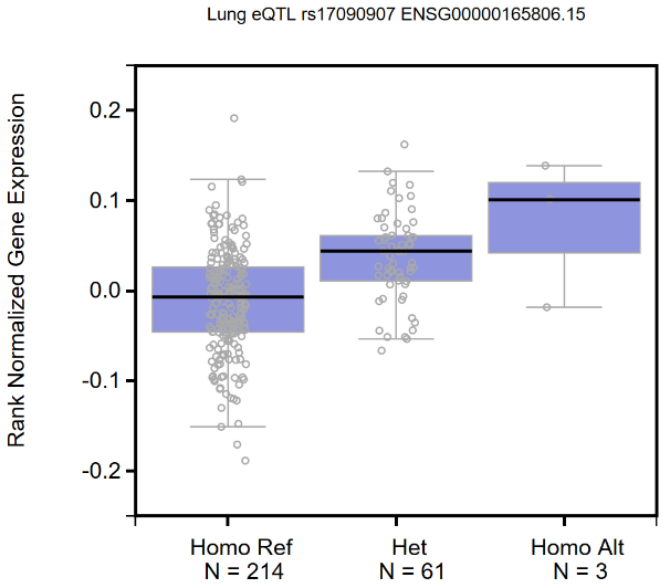


Figure 6.2: Expression quantitative trait loci (eQTLs) analysis for association of the rs17090907 genotypes with expression level of *CASP7* gene in normal lung tissue. The plot was generated by the GETx Portal (https://gtexportal.org/home/).

Another SNP that was significantly associated with survival in the LC only group was rs8192627, which is a nonsynonymous SNP located in the coding region of *TAAR8* (trace amine associated receptor 8). The rs8192627A>C produces a D-to-A or D-to-V change at amino acid position 328. *TAAR8* is a member of the *TAAR* gene family that belongs primarily to the G protein-coupled receptors (GCPR) family[571]. *TAARs* are ubiquitously expressed in human tissues, with the main expression in various brain areas[572]. Although some members of this receptor family (such as *TARR1* and *TARR4*) have been implicated in neuropsychiatric disorders, understanding of the functional role of TAAR8 is still in its infancy[573]. Therefore, further functional characterization is needed to elucidate the biological basis for this association with lung cancer survival.

The most plausible candidate was rs10218481, which was significantly associated with a decreased risk of death in both the LC only cohort (HR, 0.86; 95%CI, 0.79-0.94)

and the total cohort (HR, 0.81; 95%CI, 0.73-0.91). In the LC+COPD cohort, it showed a consistent direction of effect (HR, 0.92; 95%CI, 0.82-1.05), albeit nonsignificantly. This SNP is located within a gene desert region on chromosome 1q32.1. The *NR5A2* (nuclear receptor subfamily 5 group A member 2), approximately 7.5kb upstream of rs10218481, is the closest gene. Genetic variants in the *NR5A2* gene have been identified in genome-wide association studies to confer a risk of pancreatic cancer[574,575], and *NR5A2* gene polymorphisms were reportedly associated with the clinical outcomes in various cancer types, such as pancreatic cancer and gastric cancer[576,577]. However, the role of *NR5A2* gene has not been previously studied with respect to lung cancer. Biological experiment are necessary to determine whether this significant SNP influences the regulation of *NR5A2* gene or is linked to other functional SNPs that affect lung cancer outcome.

In the stratified analysis of the LC+COPD cohort, only one SNP, rs74798757, showed a significant association with overall survival. This SNP is located in a gene desert region on the 2p21 locus, where the nearest gene is *HAAO* (3-hydroxyanthranilate 3,4-dioxygenase), about 98kb upstream of rs74798757. Epigenetic modulations of *HAAO* gene have been reported in various types of gynecologic cancer, in which hypermethylation of *HAAO* was implicated in susceptibility to ovarian cancer and endometrial cancer[578,579]. Nevertheless, no reports are currently available on the association of rs74798757 with lung cancer survival. Moreover, none of the known lung cancer SNPs were identified in close linkage disequilibrium ($r^2 \geq 0.8$) with this variant by use of HaploReg software[580]. Thus, further deep sequencing would be warranted to identify the potential causal locus responsible for this finding.

It is noteworthy that no overlap was identified between significant SNPs in the LC+COPD cohort and in the LC only cohort, and the genotype scoring system generated based on the LC only cohort, which showed a cumulative effect on survival, was no

longer significant in the LC+COPD cohort. These results indicate the need for subphenotyping lung cancer by COPD status in genetic association analysis.

To our knowledge, the present study represents the first effort to characterize the association of genetic variations with survival in lung cancer with or without COPD. However, several limitations should be acknowledged. First, although we adopted an FDR correction approach for multiple testing, and carefully chose clinical variables to account for the potential confounding effects, false positive associations cannot be completely eliminated. Second, despite a very large and well-characterized study population (n=1,694), the relatively small group size in the LC+COPD cohort (767 vs. 927) may compromise the statistic power to detect significant associations. Third, no biological explanation for the differential SNP effects on lung cancer survival by COPD status is currently available. Nevertheless, our results will hopefully send out an important message that COPD plays a significant role in the association between genetic variations and lung cancer survival, and therefore, COPD status should be fully taken into account in future studies.

6.4 Chapter Summary

In summary, COPD status could influence the association of genetic variants with lung cancer survival. Specifically, SNP rs74798757 was significantly associated with lung cancer survival only when COPD coexisted. SNP rs10218481, *CASP7* rs17090907, *GPC5* rs1409600 and rs163933, and *TAAR8* rs8192627 had significant effects on survival in lung cancer patients who were COPD-free. Further validation of these SNP associations and functional characterization of their roles in lung cancer outcomes are warranted.

CHAPTER SEVEN

CONCLUSIONS AND FUTURE WORK

7.1 Summary of main findings

COPD and lung cancer are common respiratory diseases, and both pose a huge mortality burden on healthcare systems worldwide[295,480]. The results in present thesis suggest that not only COPD is an important comorbid disease in lung cancer, affecting near 40% to 60% of lung cancer patients, but these two diseases are closely related in the clinical setting and at the genetic level.

COPD is an independent predisposing factor for lung cancer development (Chapter 2), and both spirometric airflow limitation and radiographic emphysema have been reported to correlate with lung cancer risk[304,307]. Therefore, lung cancer prevention and screening are suggested in COPD patient population. Effective preventive measures include smoking cessation, control for secondhand tobacco smoke exposure, and several promising, albeit not well established, chemopreventive agents such as inhaled corticosteroids and statins. Although previous studies have identified a marked benefit of cancer screening in the COPD population[315,334], a number of clinical changes remain, including the common underdiagnosis and misdiagnosis of COPD, and competing causes of mortality and morbidity inherent to COPD. In addition, lung cancer in COPD appeared to be more aggressive and less likely to harbor EGFR mutations and ALK rearrangements[361]. Treatment for lung cancer coexisting with COPD is challenging as COPD may increase postoperative morbidities; therefore, precise surgical risk assessment, optimal preoperative management, and integrated multidisciplinary treatment are critically important in the perioperative setting.

There is genetic evidence linking lung cancer and COPD (Chapter 2). Previous genome-wide association studies implicate several common genetic loci that predispose individuals to both COPD and lung cancer, of which 15q25, containing nicotinic acetylcholine receptor subunit genes *CHRNA3* and *CHRNA5*, are the most well

studied[430,441]. Candidate gene studies jointly measuring genetic variation in lung cancer and COPD have also identified a number of overlapping susceptibility genes, including *HHIP*, *TERT-CLPTMA1*, and *FAM13A*[461,463,468]. Identification of the genetic links between COPD and lung cancer offers great potential for disease prevention and surveillance.

COPD is often concomitant with lung cancer but most is unrecognized[483]. Study on COPD status at lung cancer diagnosis revealed that COPD was substantially under-diagnosed in patients with early stage lung cancer, with an underdiagnosed rate of 66.8% (Chapter 3). Timing of COPD diagnosis and severity of airflow limitation were associated with overall survival and quality of life in lung cancer patients after surgery. Incidental COPD was a major factor (compared to previously recognized COPD) that increased the risk of postoperative complications and negatively impact long-term survival; thus, highlighting the importance of identification of COPD in newly diagnosed lung cancer patients. Predictors for incidental COPD were older age, male sex, lower BMI, being former and current smokers, and presenting cough, dyspnea, and hemoptysis. Patients with moderate and severe COPD had decreased lung cancer survival; however, similar survival was found between patients with mild COPD and with normal lung function, which was concordant with previous studies[408,484]. These findings suggest that pulmonary rehabilitation in moderate-to-severe COPD patients may improve their lung cancer outcomes.

Pulmonary emphysema is a crucial constituent of COPD. Previous studies revealed a strong association between lung cancer location and emphysema severity[352,353], but the prognostic value of emphysema in tumor progression remains unclear. The quantitative assessment of radiological emphysema showed that the severity of regional emphysema was associated with survival, which was independent of tumor location (Chapter 4). Regional emphysema was also predictive of quality of life related to dyspnea scale after treatment for lung cancer, with higher severity indicating worse

dyspnea. Thus, there may be a need for prophylactic management of dyspnea symptom in lung cancer patients with emphysema, in order to reduce long-term symptom burden. In addition, when tumor resection was performed in the emphysematous region, the severity of emphysema was correlated with postoperative lung function recovery; patients with moderate-to-severe emphysema might have an improvement of postoperative pulmonary ventilation capacity (i.e., lung volume reduction effect), which was in line with the previous report[391]. These findings are of prime importance to determine the indications for surgery in patients with lung cancer who have compromised lung function.

The pooled analysis of 16 previous studies, by a systematic research of PubMed database (Chapter 5), found that the presence of COPD was associated with worse survival of lung cancer across the ethnic groups studied (Asian and Caucasian). Subsequent stratified analyses demonstrated that the deleterious impact of COPD appeared to be more pronounced in patients with NSCLC, at an early-stage, and who received surgical treatment. Nevertheless, the prognostic significance of COPD in advanced stage lung cancer and SCLC needs further exploration due to the small numbers of studies in the subgroups.

Genetic associations between COPD and lung cancer risk have been well studied; however, little is known about the impact of COPD on the association of genetic variants with lung cancer survival. In the study of the 384 SNPs (Chapter 6), SNP rs74798757 was associated with overall survival in patients with lung cancer with COPD, while SNP rs10218481, *CASP7* rs17090907, *GPC5* rs1409600 and rs163933, and *TAAR8* rs8192627 had significant effects on survival in lung cancer patients who were free of COPD. The difference in genetic markers between lung cancer with and without COPD indicates that COPD status should be taken into account when attempting to identify prognostic SNP for lung cancer. Further research is necessary to validate and characterize the functional basis for the associations.

7.2 Suggestions for future work

Although results in recently published studies are intriguing and of importance to clinical practice, almost all the findings were based on a number of single-center retrospective analyses, which warrants validations based on future multi-institutional prospective studies. In addition, the actual impact of COPD in late stage lung cancer with chemotherapy remains unclear. Furthermore, there is no convincing evidence to demonstrate the efficacy of chemoprevention and screening for lung cancer in COPD patients, and the association between COPD and lung cancer mutation profile (e.g., EGFR, Kras, and ALK) is not well defined. Therefore, further research is needed to advance our understanding in these aspects of COPD-lung cancer relationship, which will ultimately improve the outcomes of this patient population.

At the genetic level, the associations between COPD, lung cancer, and survival SNPs needs further validation from independent cohorts, and the functional basis for the association of identified loci with clinical outcome in lung cancer with and without COPD requires investigations. In the era of the precision medicine, a better understanding of the clinical association and genetic basis for COPD and lung cancer may provide a unique opportunity to:

(i) optimize screening benefit from an individualized program tailored to their risks,

(ii) assist in selection of optimal treatment modalities according to the response to therapy,

(iii) refine prognostication by integration of validated genetic markers to the current predictive models, and thus to

(iv) allow allocation of limited clinical resources by means of effective surveillance for disease progression and cancer recurrence.

In addition, there is the potential to identify novel chemopreventive measures and therapeutic targets for both diseases to promote the health of the public.

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APPENDICES

Appendix A: Patient enrollment, data collection, and follow-up strategies

Since 1997, all of the new patients who had lung cancer diagnosed or confirmed at Mayo Clinic (Rochester, MN) were collected from the electronic pathology reporting system[581]. Each newly identified patient with primary lung cancer was evaluated for study eligibility and actively followed if they agree to participate in future research and give their informed consent[581].

Information abstracted from medical records for each patient included demographics (age, gender, race, education, occupation, history of tobacco exposure, and alcoholic use); history of previous diseases; lung cancer histopathology, staging, anatomical site, and treatment modalities; and family history of cancer and other medical conditions. Smoking history data were found in the patients' medical record and was confirmed with a follow-up questionnaire or an interview, encompassing age of regular smoking initiation, duration, average amount of cigarettes smoked per day, and the number of years since the patient quit smoking[582,583]. Never smokers were defined by self-report as having smoked fewer than 100 cigarettes during their lifetime. Former smokers were defined as reporting at least six months of smoking abstinence at the time of lung cancer diagnosis. Current smokers were daily cigarette smokers or those with less than six months of smoking abstinence at the time of diagnosis[582].

Histologic classification was made according to the World Health Organization's International Histological Classification of Tumors[584]. Histologic grade was evaluated as follows: well, moderately, poorly differentiated, and undifferentiated[100]. TNM stage was assigned as proposed by Mountain in 1997 (sixth edition staging system)[585] or by Detterbeck and colleagues in 2009 (seventh edition staging system)[586], dependent upon the time of lung cancer diagnosis.

All patients have been actively followed beginning at six months after diagnosis with subsequent annual follow-up by mailed questionnaires[583]. Timely verification of each patient's vital status was accomplished through the Mayo Clinic's electronic clinical notes and registration database, death certificates, next-of-kin reports, obituary documents, as well as through the Mayo Clinic Tumor Registry and Social Security Death Index website[100,581-583]. For living patients, the most up-to-date information was obtained from the last Mayo Clinic visit report or the last follow-up questionnaire, whichever was most recent. For deceased patients, the follow-up packet was sent to the next-of-kin to obtain proxy information regarding new diseases occurring after the initial diagnosis and cause of death, changes in smoking status, body weight, appetite, dietary supplements, and updated family history of lung cancer or other cancers[581,583].

All studies included in the thesis have utilized existing resources of Mayo Clinic Epidemiology and Genetic of Lung Cancer (EGLC)[587,588], which enrolled and followed all primary lung patients from 1997 to 2016.

Appendix B: Selected single nucleotide polymorphisms and survival models

Appendix Table 1: SNP selection

Chromo-some	Candidate Gene	No. of SNPs
chr 1	ALG6	2
	ATP1A4	1
	C1orf140	1
	DNM3	1
	EPB41	1
	FDPSP1	1
	IL10	1
	KLF17	1
	LOC100506985	1
	LOC100967224	1
	PTGER3	1
	PTGS2	1
	TP73	1
chr 2	ALK	1
	B3GALT1	3
	COL4A3	1
	CTNNA2	1
	GPR155	1
	LINC00570	1
	LINC01105	4
	LOC105373608	1
	LOC105374567	1
	LOC107985958	1
	MGAT5	1
	NFE2L2	1
	NRXN1	8
	THUMPD2	1
chr 3	CHL1	1
	FOXP1	2
	LINC00971	1
	LOC105374147	1
	SLC7A14	1
chr 4	IRF2	1
	KCNIP4	1

Appendix Table 1: SNP selection

Chromo-some	Candidate Gene	No. of SNPs
	LOC105374505	2
	TERT	1
chr 5	ADCY2	3
	CCNH	1
	CD74	2
	CLPTM1L	1
	LOC389273	1
	MSH3	4
	SLC6A3	1
chr 6	GCLC	4
	GLP1R	1
	LINC00472	1
	LYRM4	1
	MAP3K4	2
	PARK2	5
	PDE7B	1
	SASH1	1
	SERAC1	1
	SLC17A3	2
	TAAR8	1
chr 7	CNTNAP2	1
	CTTNBP2	1
	EGFR	1
	FAM3C	1
	GATS	1
	MAGI2	4
	MCM7	1
chr 8	CER1	1
	CHD7	1
	CSMD1	4
	FBXO25	1
	SCARA3	1
	SGCZ	2
	TNFRSF10B	4

Appendix Table 1: SNP selection

Chromo-some	Candidate Gene	No. of SNPs
	TOX	1
chr 9	ASTN2	1
	CKS2	1
	DEC1	1
	SLC24A2	2
	VPS13A	1
	XPA	1
chr 10	ABCC2	2
	CASP7	1
	LOC101929727	1
	PRKG1	1
	TRUB1	1
chr 11	CCND1	1
	CNTN5	2
	DRD4	1
	FZD4	1
	GSTP1	1
	KCNQ1	3
	LOC105376605	2
	LUZP2	1
	MTMR2	1
	RRM1	2
chr 12	CACNA1C	1
	FBXO21	2
	WIF1	1
chr 13	ABCC4	2
	BRCA2	1
	GPC5	129
	LOC105370220	1
	PARP4	1
	STARD13	1
chr 14	DHRS4L1	1
	LOC105370582	1
	PPP2R5E	1
	RGS6	10
chr 15	ATP8B4	2
	FSD2	1
	HOMER2	1
	LOC105370964	1

Appendix Table 1: SNP selection

Chromo-some	Candidate Gene	No. of SNPs
	MCTP2	3
	RYR3	1
	SYNM	1
	THSD4	3
chr 16	ABCC1	2
	WWOX	1
chr 17	ABCC3	1
chr 18	CTIF	1
	DCC	1
	DLGAP1	1
	GAREM1	1
	LOC284241	1
	PIEZO2	1
chr 19	ARHGEF18	1
	C19orf54	1
	ERCC2	1
	KXD1	2
	LEUTX	1
	PPP2R1A	1
	PRSS57	2
chr 20	CRLS1	1
	GSS	1
	LRRN4	1
	MACROD2	1
	PTPRA	1
chr 21	APP	1
	DSCAM	3
chr 22	SGSM1	1
	UPB1	1
Subtotal		332
	unknown	52
Total		384

Appendix Table 2: Quality control assessment

Chr	Total SNP	failed		call rate <0.95		MAF<0.01		HWE<10^{-4}		remaining	
		N	%	N	%	N	%	N	%	N	%
1	17	0	0.0	2	11.8	0	0.0	0	0.0	15	88.2
2	40	0	0.0	2	5.0	0	0.0	3	7.5	35	87.5
3	10	0	0.0	0	0.0	0	0.0	1	10.0	10	90.0
4	6	0	0.0	0	0.0	0	0.0	0	0.0	6	100.0
5	17	0	0.00	1	5.9	1	5.9	1	5.9	14	82.4
6	23	0	0.0	1	4.3	1	4.3	3	13.0	18	78.3
7	12	0	0.00	1	8.3	0	0.0	1	8.3	10	83.3
8	17	0	0.0	0	0.0	0	0.0	2	11.8	15	88.2
9	9	0	0.0	1	11.1	0	0.00	0	0.0	8	88.9
10	7	0	0.0	0	0.0	0	0.0	0	0.0	7	100.0
11	16	0	0.0	0	0.0	0	0.0	2	12.5	14	87.5
12	8	0	0.0	0	0.0	0	0.0	0	0.0	8	100.0
13	137	0	0.00	7	5.1	2	1.5	0	0.0	128	93.4
14	15	0	0.0	0	0.0	0	0.0	0	0.0	15	100.0
15	14	0	0.0	0	0.0	0	0.0	0	0.0	14	100.0
16	4	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0
17	2	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0
18	7	0	0.0	1	14.3	0	0.0	0	0.0	6	85.7
19	10	1	10.0	0	0.0	0	0.0	1	10.0	8	80.0
20	6	0	0.0	0	0.0	0	0.0	0	0.0	6	100.0
21	5	0	0.0	0	0.0	0	0.0	0	0.0	5	100.0
22	2	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0
overall	384	1	0.3	16	4.1	4	1.0	14	3.6	349	90.8

MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium

Appendix Table 3.1: Baseline survival model for the whole cohort

	alive/death	MST	HR (95%CI)	p
age (years)	501/1193	4.4	1.02 (1.01, 1.03)	4.2E-12
sex				
male	200/614	3.8	reference	
female	301/579	5.2	0.80 (0.72, 0.90)	1.5E-04
race				
white	480/1079	4.8	reference	
non-white	21/114	2.7	1.27 (1.04, 1.54)	1.7E-02
tumor grade				
well	196/223	10.1	reference	
moderately/poorly	305/970	3.4	1.35 (1.15, 1.58)	1.9E-04
pathological stage				
I	330/340	10.2	reference	
II	64/144	5.9	1.47 (1.21, 1.80)	1.3E-04
III	71/303	2.6	1.93 (1.60, 2.33)	7.0E-12
IV	36/406	1.6	2.81 (2.27, 3.48)	1.5E-21
therapy				
surgical treatment	447/619	8.4	reference	
non-surgical treatment	54/574	1.6	2.55 (2.15, 3.02)	5.1E-27

MST: median survival time by year; HR: hazard ratio; CI: confidence interval.

Surgical treatment including surgery alone and surgery plus adjuvant therapy; non-surgical treatment including chemotherapy, radiotherapy, chemoradiation, and other therapy.

Appendix Table 3.2: Baseline survival model for the LC+COPD cohort

	alive/death	MST	HR (95%CI)	p
age (years)	215/552	5.6	1.02 (1.01, 1.03)	2.2E-06
sex				
male	90/317	4.8	reference	
female	125/235	6.7	0.72 (0.60, 0.85)	1.8E-04
tumor grade				
well	79/108	9.1	reference	
moderately/poorly	136/444	4.3	1.31 (1.05, 1.64)	1.7E-02
pathological stage				
I	155/215	9.6	reference	
II	30/88	4.7	1.48 (1.15, 1.91)	2.2E-03
III	23/142	2.6	1.93 (1.50, 2.48)	3.3E-07
IV	7/107	1.4	2.85 (2.06, 3.94)	2.3E-10
therapy				
surgical treatment	201/368	8.2	reference	
non-surgical treatment	14/184	1.4	2.47 (1.91, 3.20)	6.6E-12

MST: median survival time by year; HR: hazard ratio; CI: confidence interval.

Surgical treatment including surgery alone and surgery plus adjuvant therapy; non-surgical treatment including chemotherapy, radiotherapy, chemoradiation, and other therapy.

Appendix Table 3.3: Baseline survival model for the LC only cohort

	alive/death	MST	HR (95%CI)	p
age (years)	286/641	3.6	1.02 (1.01, 1.03)	2.9E-06
tumor grade				
well	117/115	10.8	reference	
moderately/poorly	169/526	2.85	1.38 (1.10, 1.74)	5.8E-03
pathological stage				
I	175/125	10.9	reference	
II	34/56	6.5	1.47 (1.06, 2.03)	2.1E-02
III	48/161	2.6	2.00 (1.50, 2.66)	2.5E-06
IV	29/299	1.6	2.89 (2.14, 3.91)	6.0E-12
therapy				
surgical treatment	246/251	8.8	reference	
non-surgical treatment	40/390	1.6	2.65 (2.10, 3.330	1.7E-16

MST: median survival time by year; HR: hazard ratio; CI: confidence interval.

Surgical treatment including surgery alone and surgery plus adjuvant therapy; non-surgical treatment including chemotherapy, radiotherapy, chemoradiation, and other therapy.

Appendix Table 4.1: Individual SNPs associated with survival in the whole cohort (p<0.05)

SNP	gene	chr	best model	HR (95%CI)	p	q
rs10218481		1	Additive	0.86 (0.79, 0.94)	4.46E-04	**0.16**
rs1979100	*B3GALT1*	2	Additive	1.14 (1.04, 1.24)	5.20E-03	0.46
rs3211683	*CKS2*	9	Dominant	0.81 (0.69, 0.94)	5.70E-03	0.46
rs11659007		17	Recessive	1.34 (1.09, 1.66)	6.63E-03	0.46
rs4072556		16	Additive	0.90 (0.83, 0.97)	8.13E-03	0.46
rs215100	*ABCC1*	16	Additive	1.12 (1.03, 1.22)	1.08E-02	0.46
rs1356888	*NRXN1*	2	Dominant	0.85 (0.76, 0.96)	1.12E-02	0.46
rs8192627	*TAAR8*	6	Dominant	1.22 (1.04, 1.42)	1.38E-02	0.46
rs7432792		3	Additive	0.90 (0.83, 0.98)	1.43E-02	0.46
rs4885110		13	Additive	1.11 (1.02, 1.21)	1.55E-02	0.46
rs17469423	*SCARA3*	8	Dominant	0.84 (0.73, 0.97)	1.82E-02	0.46
rs883429	*TNFRSF10B*	8	Additive	0.89 (0.82, 0.98)	1.87E-02	0.46
rs5752019	*SGSM1*	22	Dominant	0.87 (0.78, 0.98)	1.95E-02	0.46
rs12482863	*DSCAM*	21	Dominant	0.84 (0.72, 0.97)	1.99E-02	0.46
rs74798757		2	Dominant	1.28 (1.04, 1.57)	2.06E-02	0.46
rs12609586	*PRSS57*	19	Recessive	0.81 (0.68, 0.97)	2.21E-02	0.46
rs7132154	*CACNA1C*	12	Additive	1.12 (1.02, 1.23)	2.22E-02	0.46
rs1180898	*GPC5*	13	Additive	1.10 (1.01, 1.19)	2.39E-02	0.46
rs746892	*ARHGEF18*	19	Recessive	1.19 (1.02, 1.38)	2.62E-02	0.46
rs1409600	*GPC5*	13	Dominant	0.86 (0.75, 0.98)	2.81E-02	0.46
rs2830001	*APP*	21	Dominant	0.80 (0.65, 0.98)	2.85E-02	0.46
rs3024498	*IL10*	1	Dominant	0.88 (0.78, 0.99)	2.90E-02	0.46
rs17090907	*CASP7*	10	Dominant	0.85 (0.74, 0.99)	3.21E-02	0.48
rs7359916	*PRSS57*	19	Recessive	0.81 (0.67, 0.98)	3.33E-02	0.48
rs11791132	*ASTN2*	9	Dominant	1.19 (1.01, 1.39)	3.65E-02	0.50
rs16946431	*GPC5*	13	Dominant	0.85 (0.72, 0.99)	3.82E-02	0.50
rs163933	*GPC5*	13	Dominant	0.86 (0.75, 0.99)	3.86E-02	0.50
rs1047275	*TNFRSF10B*	8	Dominant	0.88 (0.78, 1.00)	4.40E-02	0.55

Underlined numbers denote significant association at q<0.20; HR: hazard ratio; CI: confidence interval.

Appendix Table 4.2: Individual SNPs associated with survival in the LC+COPD cohort (p<0.05)

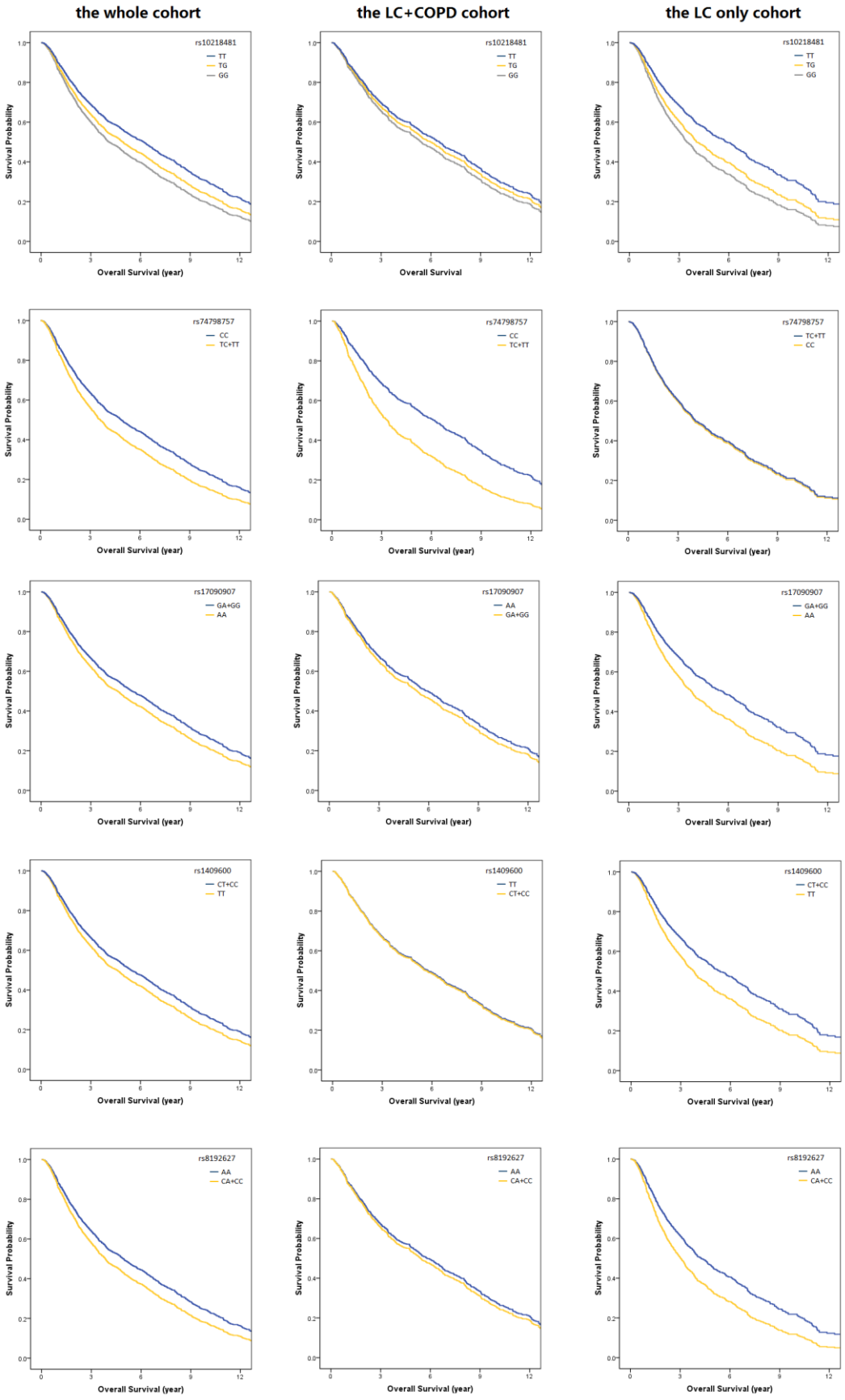
SNP	gene	chr	best model	HR (95%CI)	p	q
rs74798757		2	Dominant	1.68 (1.29, 2.20)	1.56E-04	**0.05**
rs11659007		17	Recessive	1.66 (1.22, 2.26)	1.26E-03	0.22
rs9556107	*GPC5*	13	Recessive	1.43 (1.13, 1.81)	3.30E-03	0.38
rs2209828	*GPC5*	13	Additive	1.18 (1.05, 1.32)	7.07E-03	0.53
rs3211683	*CKS2*	9	Dominant	0.75 (0.60, 0.93)	1.08E-02	0.53
rs4885110		13	Additive	1.17 (1.04, 1.33)	1.18E-02	0.53
rs62563275	*SLC24A2*	9	Dominant	1.40 (1.07, 1.84)	1.39E-02	0.53
rs12482863	*DSCAM*	21	Dominant	0.76 (0.61, 0.95)	1.50E-02	0.53
rs725040	*GPC5*	13	Recessive	1.30 (1.05, 1.62)	1.70E-02	0.53
rs1979100	*B3GALT1*	2	Additive	1.17 (1.03, 1.34)	1.78E-02	0.53
rs10092265	*CSMD1*	8	Additive	0.85 (0.75, 0.98)	2.02E-02	0.53
rs1180898	*GPC5*	13	Additive	1.16 (1.02, 1.31)	2.02E-02	0.53
rs9589446	*GPC5*	13	Recessive	1.26 (1.03, 1.54)	2.16E-02	0.53
rs9523597	*GPC5*	13	Recessive	0.68 (0.49, 0.95)	2.26E-02	0.53
rs11489584	*GATS*	7	Dominant	0.81 (0.68, 0.97)	2.27E-02	0.53
rs4072556		16	Additive	0.87 (0.77, 0.98)	2.74E-02	0.57
rs7132154	*CACNA1C*	12	Additive	1.16 (1.02, 1.33)	2.76E-02	0.57
rs746892	*ARHGEF18*	19	Recessive	1.28 (1.02, 1.61)	3.25E-02	0.61
rs17469423	*SCARA3*	8	Dominant	0.80 (0.66, 0.98)	3.34E-02	0.61
rs8075406	*ABCC3*	17	Dominant	0.83 (0.70, 0.99)	3.48E-02	0.61
rs13268772	*CSMD1*	8	Recessive	0.74 (0.56, 0.98)	3.71E-02	0.62
rs17404274		1	Dominant	1.22 (1.01, 1.48)	4.07E-02	0.64
rs847260	*RGS6*	14	Dominant	1.26 (1.01, 1.58)	4.23E-02	0.64
rs11675550	*NRXN1*	2	Dominant	1.26 (1.00, 1.58)	4.73E-02	0.69

Underlined numbers denote significant association at q<0.20; HR: hazard ratio; CI: confidence interval.

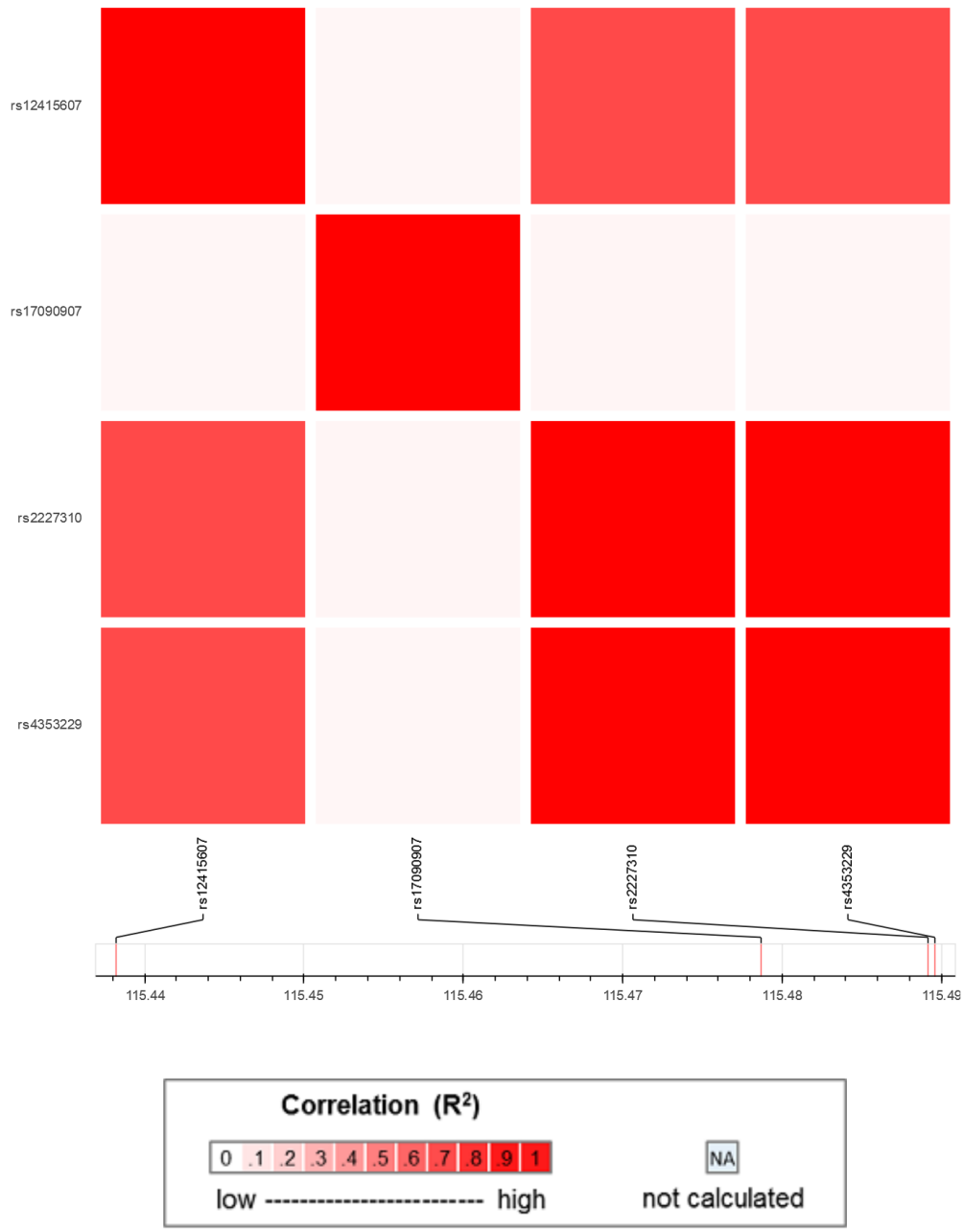
Appendix Table 4.3: Individual SNPs associated with survival in the LC only cohort (p<0.05)

SNP	gene	chr	best model	HR (95%CI)	p	q
rs10218481		1	Additive	0.81 (0.73, 0.91)	4.19E-04	**0.12**
rs17090907	*CASP7*	10	Dominant	0.71 (0.58, 0.87)	9.18E-04	**0.12**
rs1409600	*GPC5*	13	Dominant	0.73 (0.61, 0.89)	1.38E-03	**0.12**
rs163933	*GPC5*	13	Dominant	0.73 (0.60, 0.89)	1.59E-03	**0.12**
rs8192627	*TAAR8*	6	Dominant	1.41 (1.14, 1.74)	1.79E-03	**0.12**
rs9283847		6	Dominant	1.30 (1.09, 1.55)	3.86E-03	0.21
rs215100	*ABCC1*	16	Additive	1.18 (1.05, 1.33)	5.36E-03	0.21
rs6448050	*KCNIP4*	4	Dominant	0.80 (0.68, 0.94)	5.51E-03	0.21
rs16946431	*GPC5*	13	Dominant	0.73 (0.59, 0.91)	5.54E-03	0.21
rs192422272	*LINC00570*	2	Dominant	1.93 (1.19, 3.14)	8.21E-03	0.29
rs16946366	*GPC5*	13	Dominant	0.79 (0.65, 0.95)	1.32E-02	0.40
rs868678	*LOC284241*	18	Dominant	0.82 (0.70, 0.96)	1.36E-02	0.40
rs9938424	*WWOX*	16	Dominant	1.27 (1.05, 1.53)	1.58E-02	0.41
rs950725	*GPC5*	13	Additive	1.15 (1.02, 1.28)	1.73E-02	0.41
rs17655393	*FOXP1*	3	Dominant	1.21 (1.03, 1.41)	1.85E-02	0.41
rs883429	*TNFRSF10B*	8	Additive	0.86 (0.76, 0.98)	1.97E-02	0.41
rs457099		5	Additive	1.14 (1.02, 1.27)	2.30E-02	0.41
rs31490	*CLPTM1L*	5	Additive	1.14 (1.02, 1.27)	2.35E-02	0.41
rs140335	*UPB1*	22	Additive	1.14 (1.02, 1.27)	2.39E-02	0.41
rs12609586	*PRSS57*	19	Recessive	0.75 (0.58, 0.96)	2.40E-02	0.41
rs4460370	*TNFRSF10B*	8	Recessive	0.74 (0.57, 0.97)	2.69E-02	0.41
rs3024498	*IL10*	1	Dominant	0.84 (0.72, 0.98)	2.77E-02	0.41
rs7986332	*GPC5*	13	Dominant	0.76 (0.59, 0.97)	2.81E-02	0.41
rs13417432		2	Dominant	1.22 (1.02, 1.47)	2.82E-02	0.41
rs7432792		3	Additive	0.88 (0.79, 0.99)	2.96E-02	0.41
rs16958772		15	Dominant	1.20 (1.02, 1.42)	3.09E-02	0.41
rs12897719	*RGS6*	14	Dominant	1.19 (1.01, 1.39)	3.31E-02	0.43
rs4754610	*CNTN5*	11	Additive	0.87 (0.76, 0.99)	3.76E-02	0.47
rs553717	*GPC5*	13	Dominant	0.81 (0.66, 0.99)	4.13E-02	0.49
rs7999520	*GPC5*	13	Recessive	0.73 (0.54, 0.99)	4.28E-02	0.49
rs16949076	*MCTP2*	15	Dominant	1.20 (1.01, 1.43)	4.33E-02	0.49
rs16949077	*MCTP2*	15	Dominant	1.20 (1.00, 1.43)	4.81E-02	0.52

Underlined numbers denote significant association at q<0.20; HR: hazard ratio; CI: confidence interval.



Appendix Figure 1: Kaplan-Meier survival curves



Appendix Figure 2: Analysis of linkage disequilibrium