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Prevalence of Chronic Obstructive Pulmonary Disease With Lung Cancer Comorbidity: Systematic Review And Meta-Analysis

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) and lung cancer are two lung diseases with high morbidity rates in the world. Lung cancer is one of the co-morbidities in COPD and is associated with poor outcomes in COPD patients.

Methods: This is a systematic review and meta-analysis using PubMed article searches with keywords COPD, lung cancer and prevalence. Inclusion criteria are article study design either cohort retrospective/prospective or case control; article publication year from 2017-2022.

Results: Thirty-five articles in a meta-analysis found that the pooled prevalence of COPD with comorbid lung cancer was 7.87% (95% CI: 6.54%-9.3%) and statistical heterogeneity among the 35 studies was significant (I2 = 99.97%, Q = 14512.03, p = <0.001). The age of COPD patients who experienced COPD with comorbid lung cancer was above 60 years and more men than women [n=1626 (62.01%) vs n=996 (37.99%)]. Seventeen studies were based in Europe, fourteen in Asia and the remaining 4 from North America. WHO region subgroup analysis was found in the European region 7.25% (95%CI: 5.96%-8.65%), the Asian region 7% (95%CI: 4.23%-10.1%) and the North America region 10.98% (95%CI: 5.01%-17.8%).

Conclusion: The prevalence of COPD with comorbid lung cancer in this systematic review and meta-analysis was 7.87% (95% CI: 6.54%-9.3%), with characteristic as follow are more male than female; median age > 60 years, history of smoking > 30 pack years and adenocarcinoma is the most common type of lung cancer found.

Keywords:, *COPD, Lung Cancer, Prevalence*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the United States. Characterized by the presence of irreversible obstructive airflow, COPD is recognized as a systemic inflammatory disorder with various pulmonary and extrapulmonary manifestations, including an increased risk for the development of primary lung cancer. The association between COPD and lung cancer has been reported in a large number of studies and appears to be independent of the patient's age or exposure to smoking. The risk of lung cancer in patients with COPD is increased 2 to 5 times compared to smokers without COPD.

It is common knowledge that exposure to harmful gases and particles, particularly cigarette smoke, can induce both COPD and lung cancer. The Multiple Risk Factor Intervention Trial reported that patients with airflow limitation had a significantly higher prevalence of lung cancer than patients without airflow limitation with a ratio of 3.02: 0.43 per 1000 people per year. This shows that COPD patients are more likely to develop lung cancer compared to current smokers or ex-smokers with normal lung function. Although a close relationship between these two lung diseases has been observed for a long time, clarity about the molecular pathways involved and clinical correlations has only begun to be clarified in this decade.

De Torres et al reported that 215 of 2507 COPD patients had lung cancer (incidence density 16.7 cases per 1000 persons per year) with a median follow-up of 60 months. The environmental and genetics in lung cancer etiology populated conducted a control base study and a control study, namely as many as 2100 lung cancer cases and 2120 control cases. This study showed an increased risk of lung cancer in individuals with chronic bronchitis (Odd Ratio/OR 2.0, 95% Confidential Interval/CI, 15-2.5), emphysema (OR 1.9 95% CI 1.4-2, 8) and COPD (OR 2.5, 95% CI 2.0-3.1). From a 20-year follow-up study involving 448,600 nonsmokers, Turner et al also reported that new cancer mortality was significantly associated with both emphysema (Hazard ratio (HR) 1.66, 95% CI 1.06-2.59) and emphysema with

chronic bronchitis (COPD) (HR 2.44, 95% CI 1.22-4.90), but not with chronic bronchitis alone (HR 0.96, 95% CI 0.72-1.28). In both studies, COPD was diagnosed by the presence of clinical symptoms of emphysema or chronic bronchitis and a patient questionnaire, but not by spirometry or by computed tomography scan (CT-Scan).

COPD severity also influences lung cancer incidence. The First National Health and Nutrition Examination Survey collected data from 22 years of follow-up on 5402 patients and showed a positive correlation between the degree of airway obstruction and lung cancer. Data in the Multivariate proportional hazard analysis in this survey showed that mild COPD had a higher relative risk (HR 1.4 95% CI 0.8-2.6) and moderate or severe COPD had a significantly higher risk of lung cancer incidence compared with functional lung cancer. normal lung (HR 2.8, 95 CI 1.8-4.4). On the other hand, De Torres et al reported a decreased incidence of lung cancer based on the Global Initiative for Chronic Lung Disease (GOLD) grades I to IV COPD and an incidence of grade IV (92 per 1000 people per year) less than half the incidence in grade I (19,9 per year). 1000 people per year). They speculate that an active and intolerant immune system acts as a protector against the development of cancer.

Because only about 15-20% of smokers are expected to develop lung cancer with or without COPD during their lifetime, certain individuals differ in their odds of developing the disease. Cohen was the first to report on the genetic epidemiology of COPD. Patients with stage I COPD or lung cancer are at risk for airway obstruction with or without a history of smoking. Furthermore, smokers with a family history of early-stage lung cancer among stage I COPD had a higher risk of developing lung cancer than those without a family history. These findings suggest that genes may be linked to the disease.

METHODS

RESULTS

This study is the first systematic review and meta-analysis of the prevalence of COPD with comorbid lung cancer. Of the 926 articles obtained from the database and then screened through the inclusion and exclusion process, a total of 707 articles were excluded only from the title and abstract, 147 because they did not have a COPD population with comorbid lung cancer. A bias check was also carried out on articles that were screened using the Newcastle Ottawa Scale to check for research bias. So that finally 35 articles were eligible for research (Fig 1).

Table 1 shows the age characteristics of the patients, Seven studies, namely by Jing Xu et al (2018), Marton Szentkereszty (2019), Hiroyoshi Machida et al (2021), Donovan Watza et al (2020), Luo-Ching Kuo et al (2019), Ester Zamarron et al. (2021) and Shotaro Chubachi et al (2017) showed the age of COPD patients with comorbid lung cancer. The study conducted by Luo-Ching Kuo et al (2019) showed that the average age of COPD patients with comorbid lung cancer was 73.2 years old. Meanwhile, Donovan Watza et al (2020) have the lowest average age of patients at 64.6 years.

Table 2 shows the gender characteristics. Nine of the 35 articles showed the gender characteristics of COPD patients with comorbid lung cancer. Of these nine articles, 7 of them reported that COPD patients with comorbid lung cancer were more male than female. Significant differences in Hiroyoshi Machida's article, 2021, namely men n = 19, 100% vs women n = 0.0%.

Table 3 shows the patient's smoking history(pack years). Only 4 of the 35 articles reported the number of pack years of COPD patients with comorbid lung cancer. The highest number of pack years with 64.4 pack years from Shotaro Chubachi's article (2017). Meanwhile, the lowest number of pack years with 30,56 pack years from Jing Xu’s article

Table 4 shows the severity of airflow obstruction. Three articles characterize the severity of COPD. Jing Xu et al (2018) reported that of 454 COPD patients with lung cancer,

184 patients met the GOLD 1 and GOLD 2 criteria, while 270 patients met the GOLD 3 and GOLD 4 criteria. 2017), showing a similar prevalence of 7/7/1/4 and 7/8/5/1 for GOLD 1 to GOLD 4, respectively.

Table 5 shows the types of lung cancer. There are 6 articles reporting the types of lung cancer in COPD patients with comorbid lung cancer. All articles show adenocarcinoma as the most common type of lung cancer, followed by squamous type. Donovan Watza et al, 2020 reported as many as 330 adenocarcinomas from 677 COPD patients with comorbid lung cancer.

Table 6 shows the overall survival of the patients. Only 1 article out of 35 reported the survival of COPD patients with comorbid lung cancer, namely Marton Szentkereszty, 2019 with a median overall survival of 16.9 months.

Table 7 shows the patient's COPD phenotype. Two of the 35 articles reported the type of COPD phenotype in COPD patients with comorbid lung cancer. Both articles reported that all COPD patients with comorbid lung cancer had an emphysema phenotype.

Table 8 shows the distribution of COPD prevalence with comorbid lung cancer. Meta-analysis in 35 studies found that the pooled prevalence of COPD with comorbid lung cancer was 7.87% (95% CI: 6.54%-9.3%) and statistical heterogeneity among the 35 studies was significant (I^2 = 100%, Q = 14512.03, p = <0.001).

Table 9 shows the prevalence of COPD with comorbid lung cancer by study period. The research time period was obtained from 35 articles, the longest research by Magnus Ekstrom et al, 2017 in 1990 to 2013 for 24 years. Further research by Misako Nagasaka et al, 2020 for 23 years (1993-2015) and Luo-Ching Kuo et al, 2019 for 18 years (1996-2013), while the shortest research is Jing Xu et al, 2018 (2915-2016) and Timm Greulich et al, 2017 (2013-2014) for 2 years. The results of the analysis and forest plots are presented in tables and figures. Meta-analysis of subgroups based on the study period found the prevalence of COPD based on the subgroup study period < 5 years was 13.65% (95% CI: 9.23%-18.43% and the prevalence

in the study 5 years was 4.92% (95 %CI: 3.38%-6.64%. The statistical heterogeneity of the subgroups was very significant (I2 = 99.7%, Q = 14512.03, p=<0.001).

Table 10 shows the subgroups by WHO region. According to the World Health Organization (WHO) Region, 17 of the 35 studies were conducted in Europe, 14 were conducted in Asia and the remaining 4 were conducted in North America. Meta-analysis of subgroups based on WHO region found the prevalence of COPD with comorbid lung cancer based on WHO subgroup Europe region 7.25% (95%CI: 5.96%-8.65%), Asia subgroup 7% (95%CI: 4 .23%-10.1%) and the North America region subgroup 10.98% (95%CI: 5.01%-17.8%).

Table 11 shows the subgroups based on the study design. Eighteen of 35 studies were prospective cohort designs. While the study with a retrospective cohort design consisted of 14 studies and 3 were case controls. Meta-analysis of subgroups based on study design found the prevalence of COPD with comorbid lung cancer based on the prospective cohort study design was 4.98% (95% CI: 3.59%-6.53%), the retrospective cohort subgroup was 5.34% (95 %CI:3.9%-6.94%) and the case control subgroup was 58.09%(95%CI:44.56%-71.31%). Subgroup statistical heterogeneity was very significant (I2 = 99.77%, Q = 14512.03, p = <0.001)

DISCUSSION

This study is the first systematic review and meta-analysis of the prevalence of COPD with lung cancer comorbidity. Of the 926 articles obtained from the database then screened through the inclusion and exclusion process, 707 articles were excluded only from the title and abstract, 147 because they did not have a COPD population with lung cancer comorbidity. Bias examination was also carried out on the articles that were screened, namely with the Newcastle Ottawa Scale to check for research bias. So that finally 35 articles were eligible for research.

The pooled prevalence of COPD with lung cancer comorbidity was 7.87% (95%CI: 6.54%-9.3%). The sample size of COPD with lung cancer comorbidity varied from 6 to 4138.

Statistical heterogeneity among the 35 studies was significant ($I2 = 100\%$, $Q = 14512.03$, $p = <0.001$) because in addition to being influenced by the number of samples, it is likely influenced by the characteristics of the population in the country, the length of the study or the location of the study, for example, only a single center or multicenter.

Evidence linking COPD to the development of lung cancer has been studied from various studies such as population-based, through lung cancer screening or *case-control studies* . Jie Dai et al., 2017, reported that *the magnitude* of the association between COPD and lung cancer is influenced by gender, smoking habits or history of other respiratory diseases.

In this study, there are 3 studies that show the age characteristics of COPD patients with lung cancer comorbidities. The average age is over 65 years . Sharma and Goodwin, 2006, lung aging is associated with changes in structural *remodeling* , decreased respiratory function and increased susceptibility to respiratory diseases, both acute and chronic. Even in healthy humans, lung function will decline with increasing age. Janssens et al., 1999 reported that tidal volume, increased respiratory rate and maximum aerobic capacity decreased with increasing age.

Evidence suggests that the elastic recoil capacity of the lung is related to structural *remodeling* by the extracellular matrix in the lung parenchyma and decreases *forced expiratory volume* in old age. The *Burden of Obstructive Lung Disease* (BOLD) study showed that people over 70 years of age have a greater likelihood of developing COPD (Buist et al., 2007). Meanwhile, Federico et al. (2016) the median age of lung cancer is around 70 years and 68% of patients are diagnosed with lung cancer after the age of 65 years.

For gender characteristics, seven of the nine studies reported that men had more COPD with comorbid lung cancer. Jafri et al., 2021 reported that COPD is considered a disease closely related to men, although this is associated because men smoke more than women, although the prevalence of smokers in women is around 28%. The global female population is

larger than men, but is still *under diagnosed* and *under researched* on COPD studies. Silvia Novella et al. 2018, reported that in 2013, lung cancer was associated with 26% of cancer deaths in women while 28% in men.

Four of the 35 articles reported the number of *pack years* in COPD patients with comorbid lung cancer. Hiroyoshi Machida et al., 2021 reported the highest number of *pack years* with 62.7 *pack years* , while the lowest was reported in Jing Xu et al., 2018 at 30.54 pack years. The risk of lung cancer is known to increase with increasing smoking frequency. As many as 92.7% of cancers occur in heavy smokers with a median of 21.3 *pack years* . Patients who started smoking under 20 years had a 22% higher prevalence of COPD than those who started smoking over 20 years. A study of 8045 healthy individuals followed for 25 years, the incidence of COPD in non-smokers was very low (1% COPD GOLD stage II or more) compared to 27% in active smokers.

For the severity of COPD patients with comorbid lung cancer, only 3 studies reported this. Hiroyoshi Machida et al.'s 2018 study with results of 7/7/1/4 (GOLD 1/GOLD 2/GOLD 3/GOLD 4). These results are not much different from the study by Shotaro Chibachi, 2017 with results of 7/8/5/1. Elena ddk, 2020 reported that mortality predictions were influenced by the severity of COPD. Based on her research, in GOLD D, five consecutive years of mortality from GOLD 1 to 4 were 16.7%, 39.1%, 29.5% and 46%. In addition to being influenced by the degree of airway obstruction, mortality is also influenced by the frequency of exacerbations.

Many studies have investigated the risk of developing lung cancer in COPD patients. Several studies have examined the role of genetic loci in the susceptibility of COPD patients to develop lung cancer. Young et al conducted a study linking the role of genetic loci to COPD patients in the Caucasian population of smokers in New Zealand. One of the genes that is quite susceptible is the rs2808630 locus. In addition, Yang et al also studied the CHRNA3 gene which is a risk of developing lung cancer in COPD patients in the smoking population in China.

Donovan Watza et al in their study concluded that there were at least 6 of the 29 *single nucleotide polymorphisms* (SNPs), namely rs868936562, rs61505577, rs72969686, rs73783372, rs1074822 and rs61731180 which had a risk of developing lung cancer in COPD patients. In our study, six of the 35 articles reported the type of lung cancer in COPD patients with comorbid lung cancer. The most common type of lung cancer is adenocarcinoma, followed by squamous carcinoma, non-small cell carcinoma and the last is large cell carcinoma.

Only 1 article reported on median survival, namely Marton et al., 2019 with *an overall survival* of 16.9%. However, in this study, no *head-to-head comparison was conducted* between patients with COPD alone and COPD patients with comorbid lung cancer. However, when compared with patients with cancer alone, the overall survival was 11 months, so it can be concluded that COPD patients with comorbid lung cancer have worse survival.

Two of the 35 articles reported the phenotype of COPD with COPD comorbidities. Both the studies by Cecilia Mouronte-Robias et al., 2018 and Karina Portillo et al., 2017 reported that all samples were patients with emphysema phenotype. This is because both studies did take samples with the type of emphysema so that it can be ascertained that all samples were emphysema types. Cecilia Mouronte-Robias et al., 2018 reported that there was a relationship between the type of emphysema and lung cancer in COPD patients. The centrilobular type was most often found, followed by the paraseptal type of emphysema. Centrilobular emphysema is usually associated with older age, higher smoking frequency and more severe COPD. In this study, COPD patients with lung cancer had a predominant location of emphysema in the superior lobe. Some clinical evidence suggests that emphysema and the severity of the obstructive degree increase the risk of lung cancer more than the effects of smoking.

For subgroup analysis divided based on research period, WHO regions and research design. Subgroup analysis based on research period obtained the longest research by Magnus

Ekstrom et al., 2017 in 1990 to 2013 for 24 years and the shortest was Jing Xu et al., 2018 (2015-2016) and Timm Greulich et al., 2017 (2013-2014) for 2 years. The prevalence of COPD with lung cancer comorbidity based on the subgroup of the study period <5 years was 13.65% (95%CI: 9.23%-18.43%) and the prevalence of COPD with lung cancer comorbidity ≥ 5 years was 4.92% (95%CI: 3.38%-6.64%). Although the number of research samples ≥ 5 years was more than the study <5 years, in terms of prevalence, the study <5 years had a higher prevalence than ≥ 5 years . This also causes significant heterogeneity between studies (I2 = $^{99.77}$ %, Q = 14512.03, p = <0.001). Song Vogue Ahn et al., 2020, one of the researchers with a research period of ≥ 5 years (2004-2015) put forward factors that influence the development of lung cancer in COPD patients, namely old age, male, low *body mass index* (BMI), history of hypertension, history of diabetes mellitus, endurance exercise and history of smoking.

The link between COPD and lung cancer has been widely described. Repeated damage and repair by chronic inflammation and frequent exacerbations of COPD result in tissue damage and DNA damage, leading to malignant cell transformation and development of lung cancer.

The next subgroup analysis is based on WHO region. A total of 17 studies were conducted in Europe, 14 in Asia and 4 in North America. Interestingly, the North American subgroup has the highest prevalence of 10.98% (95%CI: 5.01%-17.80%) , then the European subgroup with 7.25% (95%CI: 5.96%-8.65%) and the Asian subgroup 7.00% (95%CI: 4.23%-10.10%). The contributing countries of the WHO North American region are the United States and Canada. Data from *the American Lung Association* in 2018 stated that 16.5 million people or 6.6% were reported to have COPD (both chronic bronchitis and emphysema) with the state of Wisconsin the most (15.3%). During 2007-2010, around 8.5 million people were reported to have COPD. However, this figure may represent an *under diagnosis* because more than 18 million have evidence of impaired lung function consistent with COPD.

The next subgroup analysis is the study design subgroup. The prevalence of COPD with lung cancer comorbidity based on the prospective cohort study design was 4.98% (95%CI: 3.59%-6.53%), the retrospective cohort subgroup was 5.34% (95%CI: 3.9%-6.94%) and the case-control subgroup was 58.09% (95%CI: 44.56%-71.31%). The high prevalence in the *case-control subgroup* was due to the research method which specifically targeted samples consisting of patients with COPD and lung cancer.

CONCLUSION

The prevalence of COPD with comorbid lung cancer in this systematic review and meta-analysis was 7.87% (95% CI: 6.54%-9.3%), with characteristic as follow are more male than female; median age > 60 years, history of smoking > 30 pack years and adenocarcinoma is the most common type of lung cancer found.

CONFLICT OF INTEREST

The process of activities and writing of the results of this research was carried out independently. Research costs are entirely from the author's funds. So that it can be ascertained that there.

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SUPPLEMENTARY

Table 1. Age characteristics of COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	Age (mean), year
1	Jing Xu, 2018	454	70,74 ± 10,39
2	Marton Szentkereszty, 2019	80	65,3 ± 0,9
3	Hiroyoshi Machida , 2021	19	72,4 ± 7,1
4	Donovan Watza, 2020	677	64,6
5	Luo-Ching Kuo, 2019	561	73,2 ± 9,98
6	Ester Zamarron, 2021	47	66 ± 10
7	Shotaro Chubachi, 2017	21	73,4 ± 7,2

Table 2. Gender of COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	Gender	
			Male (%)	Female (%)
1	Cecilia Mouronte-Robias, 2018	169	122 (72,2)	47 (27,8)
2	Jing Xu, 2018	454	339 (74,7)	115 (25,3)
3	Martin Sandelin, 2018	594	291 (49)	303 (51)
4	Marton Szentkereszty, 2019	80	50 (62,5)	30 (37,5)
5	Hiroyoshi Machida, 2021	19	19 (100)	0 (0)
6	Donovan Watza, 2020	677	291 (43)	386 (57)
7	Luo-Ching Kuo, 2019	561	454 (76,4)	107 (23,6)
8	Ester Zamarron, 2021	47	41 (87,2)	6 (12,8)
9	Shotaro Chubachi, 2017	21	19 (90,5)	2 (9,5)

Table 3. Characteristics of pack years of COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	*Pack years*
1	Jing Xu, 2018	454	30,56
2	Hiroyoshi Machida, 2021	19	62,7
3	Donovan Watza, 2020	677	50,5
4	Shotaro Chubachi, 2017	21	64,4

Table 4. Characteristics of the severity of COPD in COPD patients with comorbid lung cancer

No	Author, year	COPD Severity

		Total COPD population with comorbid lung cancer	Gold 1	Gold 2	Gold 3	Gold 4
1	Jing Xu, 2018	454	184		270	
2	Hiroyoshi Machida, 2021	19	7	7	1	4
3	Shotaro Chubachi, 2017	21	7	8	5	1

Table 5. Characteristics of lung cancer types in COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	Type of lung cancer				
			Adenocarcinoma	Squamous	Large cell	Small cell lung carcinoma	Other type
1	Cecilia Mouronte-Robias, 2018	169	70	58	0	28	13
2	Marton Szentkereszty, 2019	80	60	20	0	0	0
3	Hiroyoshi Machida dkk, 2021	19	6	3	0	2	8
4	Donovan Watza, 2020	677	330	173	0	105	69
5	Karina Portillo, 2017	6	3	0	0	0	3
6	Tamami Sakai, 2020	97	42	36	1	10	8

Table 6. Characteristics of average survival/overall survival in COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	Overall survival (median OS), month
1	Marton Szentkereszty, 2019	80	16,9

Table 7. Types of COPD phenotype in COPD patients with comorbid lung cancer

No	Author, year	Total COPD population with comorbid lung cancer	Emphysema	Chronic bronchitis
1	Cecilia Mouronte-Robias, 2018	169	169	0
2	Karina Portillo, 2017	6	6	0

Table 8. Prevalence of COPD with comorbid lung cancer

No	Author, year	Prevalence	95% CI	Weight (%)
1	Ane Aamli Gagnat, 2018	7,11%	4,84%-9,77%	2,74
2	Song Voque, 2020	9,81%	9,27%-10,36%	3,02
3	Youngmee Kim, 2021	1,62%	1,41%-1,85%	3,02
4	Samy Suissa, 2019	1,64%	1,54%-1,74%	3,03
5	Misako Nagasaka, 2020	3,46%	3,08%-3,86%	3,02
6	Cecilia Mouronte-Robias, 2018	69,55%	63,60%-75,19%	2,56
7	Jing Xu, 2018	44,64%	41,60%-47,71%	2,91
8	Magnus Ekstrom, 2017	5,44%	3,23%-8,17%	2,67
9	Martin Sandelin, 2018	2,99%	2,75%-3,23%	3,03
10	Marton Szentkereszty, 2019	59,70%	51,25%-67,88%	2,28
11	Haval Balata, 2020	6,95%	4,82%-9,42%	2,77
12	Hye Yun Park, 2020	0,49%	0,44%-0,55%	3,03
13	Hiroyoshi Machida, 2021	8,48%	5,15%-12,52%	2,53
14	AJN Raymakers, 2020	2,49%	2,34%-2,65%	3,03
15	Hye In Jung, 2018	4,72%	4,40%-5,06%	3,02
16	Gunnar R, Husebo, 2019	6,47%	4,33%-8,99%	2,75
17	Donovan Watza, 2020	60,28%	57,41%-63,13%	2,92
18	Ana Rute Costa, 2021	2,66%	2,18%-3,19%	3,00
19	Luo-Ching Kuo, 2019	6,10%	5,62%-6,60%	3,02
20	Karina Portillo, 2017	20,69%	7,61%-37,61%	1,21
21	Timm Greulich, 2017	1,82%	1,75%-1,89%	3,03
22	Ester Zamarron, 2021	5,54%	4,10%-7,19%	2,88
23	Hye Yun Park, 2020	6,89%	6,35%-7,45%	3,02
24	Josep Montserrat-Capdevila, 2021	2,29%	2,10%-2,48%	3,03
25	Yong Suk Jo, 2020	8,33%	7,90%-8,78%	3,02
26	Chieh-Mo Lin, 2020	6,76%	6,56%-6,97%	3,03
27	Chloe I. Bloom, 2018	4,48%	4,35%-4,61%	3,03
28	Youngmee Kim, 2021	1,06%	0,89%-1,24%	3,02
29	Shotaro Chubachi, 2017	4,83%	2,99%-7,06%	2,75
30	Philip W Atone, 2020	2,32%	2,22%-2,43%	3,03
31	Renata Rubinsztajn, 2018	2,48%	1,21%-4,16%	2,76

32	Bjorn Stallberg, 2018	6,24%	5,89%-6,61%	3,02
33	Elena Jureviciene, 2022	3,85%	3,32%-4,41%	3,00
34	Hok Sum Chan, 2018	2,49%	2,19%-2,80%	3,02
35	Tamami Sakai, 2020	18,80%	15,54%-22,29%	2,79
Pooled		**7,87%**	**6,54%-9,30%**	**100**
Statitstic				
I2		99,77	99,75-99,78	
Cochran's Q		14512,03		
Chi2, p		<0,001		

Table 9. Prevalence of COPD with comorbid lung cancer based research period subgroup

Author, year	Prevalence	95% CI	Weight (%)
Research period < 5 years			
Ane Aamli Gagnat, 2018	7,11%	4,84%-9,77%	2,74
Youngmee Kim, 2021	1,62%	1,41%-1,85%	3,02
Cecilia Mouronte-Robias, 2018	69,55%	63,60%-75,19%	2,56
Jing Xu, 2018	44,64%	41,60%-47,71%	2,91
Marton Szentkereszty, 2019	59,70%	51,25%-67,88%	2,28
Gunnar R, Husebo, 2019	6,47%	4,33%-8,99%	2,75
Timm Greulich, 2017	1,82%	1,75%-1,89%	3,03
Yong Suk Jo, 2020	8,33%	7,90%-8,78%	3,02
Shotaro Chubachi, 2017	4,83%	2,99%-7,06%	2,75
Elena Jureviciene, 2022	3,85%	3,32%-4,41%	3,00
Hok Sum Chan, 2018	2,49%	2,19%-2,80%	3,02
Research period < 5 years subgroup	**13,65%**	**9,23%-18,43%**	**31,09**
Research period ≥ 5 years			
Song Voque, 2020	9,81%	9,27%-10,36%	3,02
Samy Suissa, 2019	1,64%	1,54%-1,74%	3,03
Misako Nagasaka, 2020	3,46%	3,08%-3,86%	3,02
Magnus Ekstrom, 2017	5,44%	3,23%-8,17%	2,67
Martin Sandelin, 2018	2,99%	2,75%-3,23%	3,03
Hye Yun Park, 2020	0,49%	0,44%-0,55%	3,03
Hiroyoshi Machida, 2021	8,48%	5,15%-12,52%	2,53
Ana Rute Costa, 2021	2,66%	2,18%-3,19%	3,00
Luo-Ching Kuo, 2019	6,10%	5,62%-6,60%	3,02
Karina Portillo, 2017	20,69%	7,61%-37,61%	1,21
Ester Zamarron, 2021	5,54%	4,10%-7,19%	2,88
Hye Yun Park, 2020	6,89%	6,35%-7,45%	3,02
Josep Montserrat-Capdevila, 2021	2,29%	2,10%-2,48%	3,03
Chieh-Mo Lin, 2020	6,76%	6,56%-6,97%	3,03
Chloe I. Bloom, 2018	4,48%	4,35%-4,61%	3,03
Youngmee Kim, 2021	1,06%	0,89%-1,24%	3,02
Tamami Sakai, 2020	18,80%	15,54%-22,29%	2,79
Research period ≥ 5 years subgroup	**4,92%**	**3,38%-6,64%**	**48,35**
Unknown research period			
Haval Balata, 2020	6,95%	4,82%-9,42%	2,77

AJN Raymakers dkk, 2020	2,49%	2,34%-2,65%	3,03
Hye In Jung, 2018	4,72%	4,40%-5,06%	3,02
Donovan Watza, 2020	60,28%	57,41%-63,13%	2,92
Philip W Atone, 2020	2,32%	2,22%-2,43%	3,03
Renata Rubinsztajn, 2018	2,48%	1,21%-4,16%	2,76
Bjorn Stallberg, 2018	6,24%	5,89%-6,61%	3,02
Unknown research period subgroup	**8,68%**	**5,21%-12,55%**	**20,56**
Pooled	**7,87%**	**6,54%-9,30%**	**100,00**
I-squared	99,77	99,75-99,78	
Cochran's Q	14512,03		
Chi2, P	<0,001		

Table 10. Prevalence of COPD with comorbid lung cancer based WHO region subgroup

Author, year	Prevalence	95% CI	Weight (%)
Asia			
Song Voque, 2020	9,81%	9,27%-10,36%	3,02
Youngmee Kim, 2021	1,62%	1,41%-1,85%	3,02
Jing Xu, 2018	44,64%	41,60%-47,71%	2,91
Hye Yun Park, 2020	0,49%	0,44%-0,55%	3,03
Hiroyoshi Machida, 2021	8,48%	5,15%-12,52%	2,53
Hye In Jung, 2018	4,72%	4,40%-5,06%	3,02
Luo-Ching Kuo, 2019	6,10%	5,62%-6,60%	3,02
Hye Yun Park, 2020	6,89%	6,35%-7,45%	3,02
Yong Suk Jo, 2020	8,33%	7,90%-8,78%	3,02
Chieh-Mo Lin, 2020	6,76%	6,56%-6,97%	3,03
Youngmee Kim, 2021	1,06%	0,89%-1,24%	3,02
Shotaro Chubachi, 2017	4,83%	2,99%-7,06%	2,75
Hok Sum Chan, 2018	2,49%	2,19%-2,80%	3,02
Tamami Sakai, 2020	18,80%	15,54%-22,29%	2,79
Asia subgroup	**7,00%**	**4,23%-10,10%**	**41,21**
Eropa			
Ane Aamli Gagnat, 2018	7,11%	4,84%-9,77%	2,74
Cecilia Mouronte-Robias, 2018	69,55%	63,60%-75,19%	2,56
Magnus Ekstrom, 2017	5,44%	3,23%-8,17%	2,67
Martin Sandelin, 2018	2,99%	2,75%-3,23%	3,03
Marton Szentkereszty, 2019	59,70%	51,25%-67,88%	2,28
Haval Balata, 2020	6,95%	4,82%-9,42%	2,77
Gunnar R, Husebo, 2019	6,47%	4,33%-8,99%	2,75
Ana Rute Costa, 2021	2,66%	2,18%-3,19%	3,00
Karina Portillo, 2017	20,69%	7,61%-37,61%	1,21
Timm Greulich, 2017	1,82%	1,75%-1,89%	3,03
Ester Zamarron, 2021	5,54%	4,10%-7,19%	2,88
Josep Montserrat-Capdevila, 2021	2,29%	2,10%-2,48%	3,03
Chloe I. Bloom, 2018	4,48%	4,35%-4,61%	3,03
Philip W Atone, 2020	2,32%	2,22%-2,43%	3,03
Renata Rubinsztajn, 2018	2,48%	1,21%-4,16%	2,76
Bjorn Stallberg, 2018	6,24%	5,89%-6,61%	3,02
Elena Jureviciene, 2022	3,85%	3,32%-4,41%	3,00

Europe subgroup	**7,25%**	**5,96%-8,65%**	**46,80**
North America			
Samy Suissa, 2019	1,64%	1,54%-1,74%	3,03
Misako Nagasaka, 2020	3,46%	3,08%-3,86%	3,02
AJN Raymakers, 2020	2,49%	2,34%-2,65%	3,03
Donovan Watza, 2020	60,28%	57,41%-63,13%	2,92
North America subgroup	**10,98%**	**5,01%-17,80%**	**11,99**
Pooled	**7,87%**	**6,54%-9,30%**	**100,00**
Statistics			
I-squared	99,77	99,75-99,78	
Cochran's Q	14512,03		
Chi2, P	<0,001		

Table 11. Survival Time Analysis based on the number of chemotherapy cycles

Author, year	Prevalence	95% CI	Weight (%)
Cohort Retrospective			
Ane Aamli Gagnat, 2018	7,11%	4,84%-9,77%	2,74
Hye In Jung, 2018	4,72%	4,40%-5,06%	3,02
Ana Rute Costa, 2021	2,66%	2,18%-3,19%	3,00
Luo-Ching Kuo, 2019	6,10%	5,62%-6,60%	3,02
Karina Portillo, 2017	20,69%	7,61%-37,61%	1,21
Timm Greulich, 2017	1,82%	1,75%-1,89%	3,03
Hye Yun Park, 2020	6,89%	6,35%7,45%	3,02
Chieh-Mo Lin, 2020	6,76%	6,56%-6,97%	3,03
Youngmee Kim, 2021	1,06%	0,89%-1,24%	3,02
Philip W Atone, 2020	2,32%	2,22%-2,43%	3,03
Bjorn Stallberg, 2018	6,24%	5,89%-6,61%	3,02
Elena Jureviciene, 2022	3,85%	3,32%-4,41%	3,00
Hok Sum Chan, 2018	2,49%	2,19%-2,80%	3,02
Tamami Sakai, 2020	18,80%	15,54%-22,29%	2,79
Cohort Retrospective subgroup	**4,98%**	**3,59%-6,53%**	**39,96**
Cohort Prospective			
Song Voque, 2020	9,81%	9,27%-10,36%	3,02
Youngmee Kim, 2021	1,62%	1,41%-1,85%	3,02
Samy Suissa, 2019	1,64%	1,54%-1,74%	3,03
Misako Nagasaka, 2020	3,46%	3,08%-3,86%	3,02
Magnus Ekstrom, 2017	5,44%	3,23%-8,17%	2,67
Martin Sandelin, 2018	2,99%	2,75%-3,23%	3,03
Marton Szentkereszty, 2019	59,70%	51,25%-67,88%	2,28
Haval Balata, 2020	6,95%	4,82%-9,42%	2,77
Hye Yun Park, 2020	0,49%	0,44%-0,55%	3,03
Hiroyoshi Machida, 2021	8,48%	5,15%-12,52%	2,53
AJN Raymakers, 2020	2,49%	2,34%-2,65%	3,03
Gunnar R, Husebo, 2019	6,47%	4,33%-8,99%	2,75
Ester Zamarron, 2021	5,54%	4,10%-7,19%	2,88
Josep Montserrat-Capdevila, 2021	2,29%	2,10%-2,48%	3,03
Yong Suk Jo, 2020	8,33%	7,90%-8,78%	3,02
Chloe I. Bloom, 2018	4,48%	4,35%-4,61%	3,03
Shotaro Chubachi, 2017	4,83%	2,99%-7,06%	2,75
Renata Rubinsztajn, 2018	2,48%	1,21%-4,16%	2,76

Cohort Prospective subgroup	5,34%	3,90%-6,94%	51,65
Case Control			
Cecilia Mouronte-Robias, 2018	69,55%	63,60%-75,19%	2,56
Jing Xu, 2018	44,64%	41,60%-47,71%	2,91
Donovan Watza, 2020	60,28%	57,41%-63,13%	2,92
Case Control subgroup	58,09%	44,56%-71,31%	8,39
Pooled	7,87%	6,54%-9,30%	100
Statistics			
I-squared	99,77	99,75-99,78	
Cochran's Q	14512,03		
Chi2, P	<0,001		

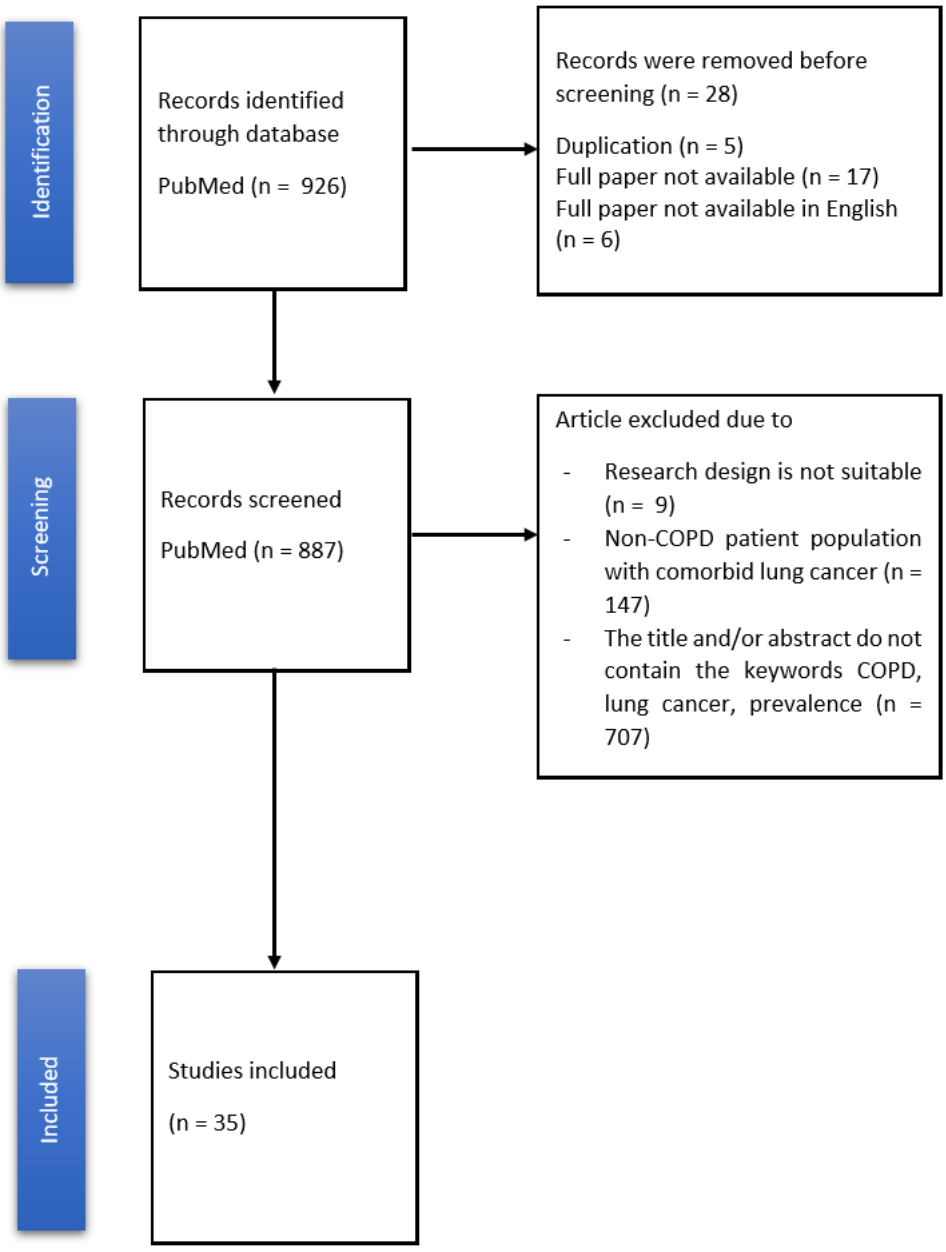

Figure 1. PRISMA 2020 Flow Diagram

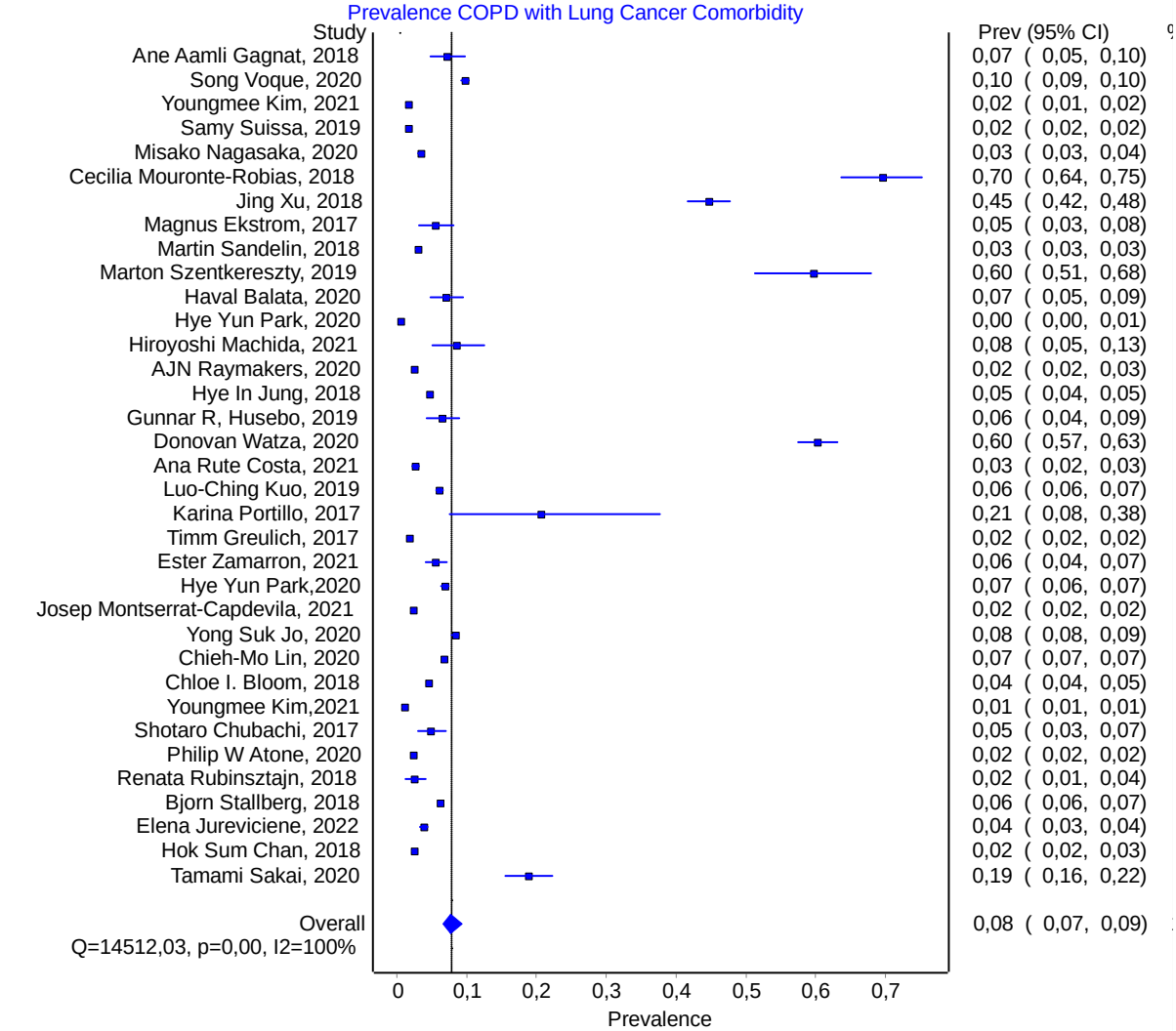

Figure 2. Forest plot of COPD prevalence with comorbid lung cancer

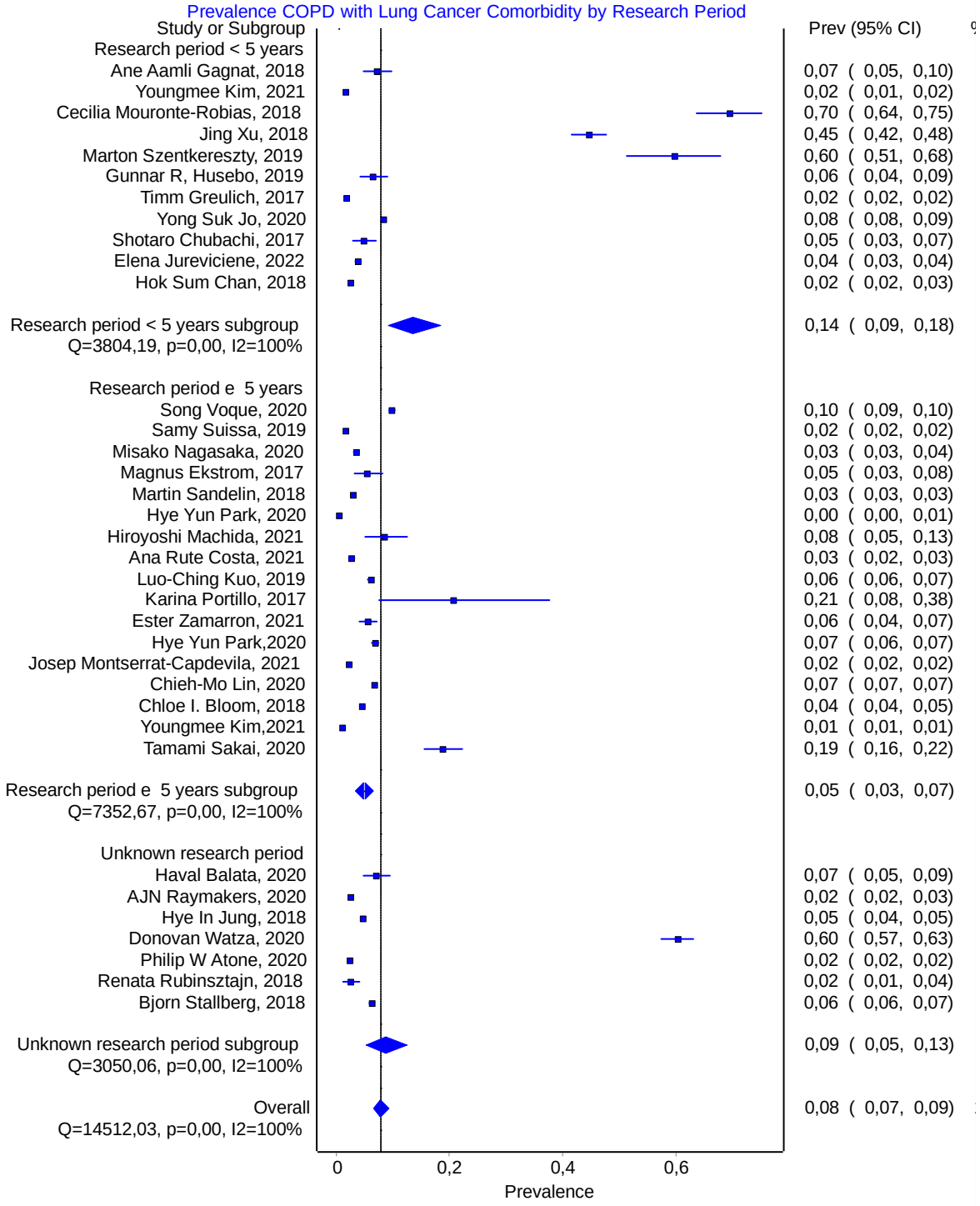

Figure 3. Forest plot of COPD prevalence with comorbid lung cancer based research period subgroup

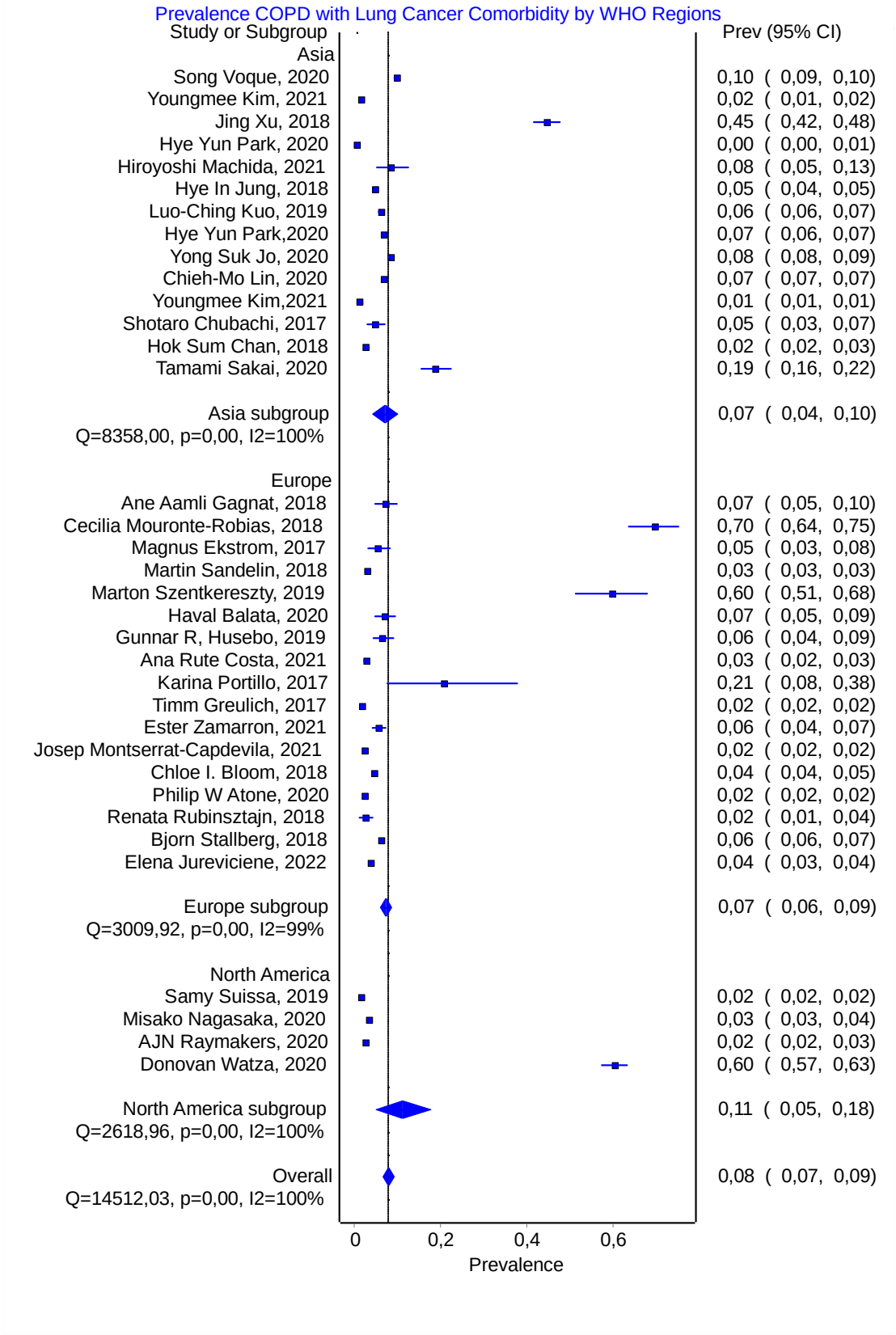

Figure 4. Forest plot of COPD prevalence with comorbid lung cancer based WHO regions subgroup

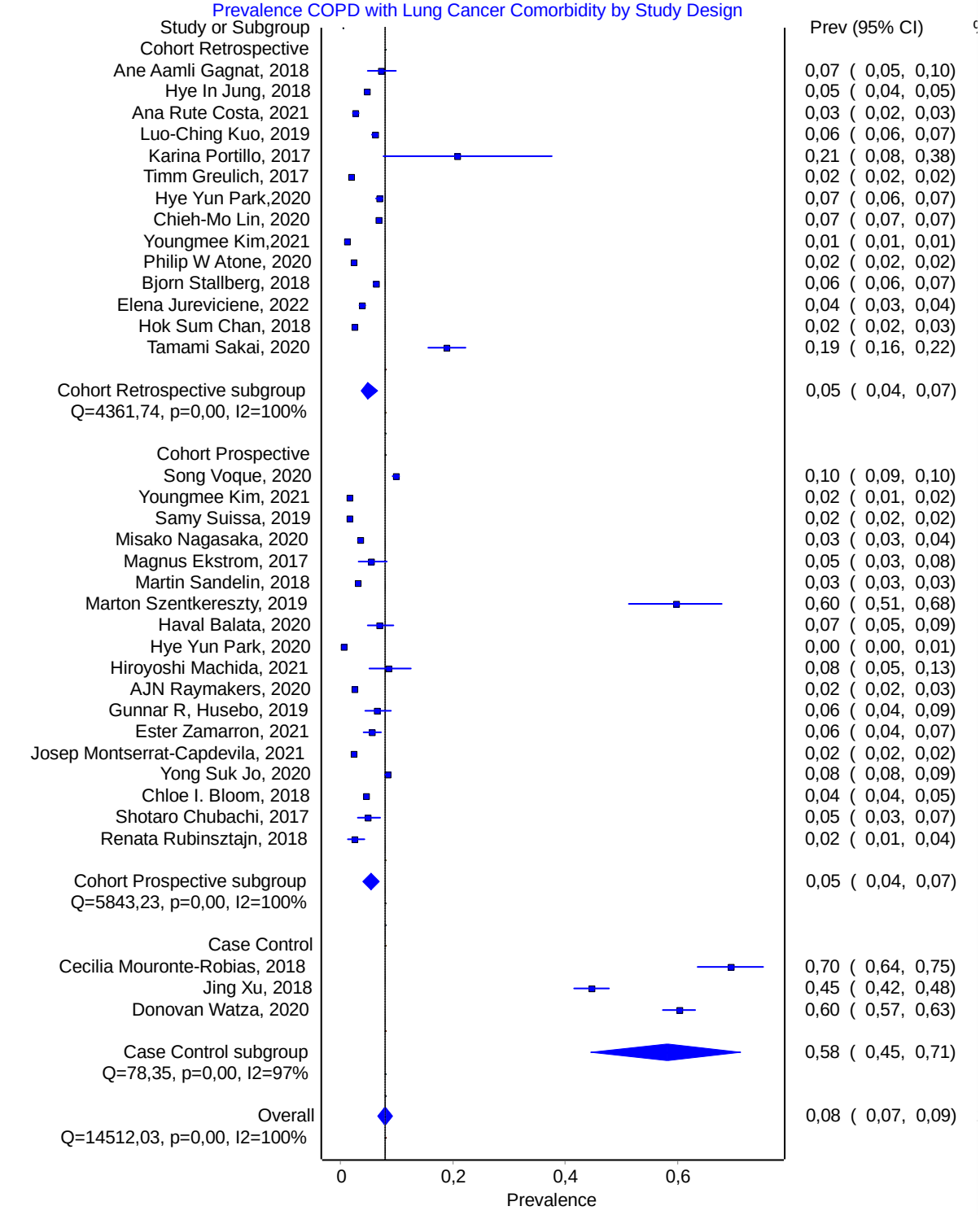

Figure 5. Forest plot of COPD prevalence with comorbid lung cancer based study design subgroup

Table 12. Newcastle Ottawa Scale Article Bias Assessment

No	Article Title	First Author, year publication	Selection	Comparability	Output	Score total	Interpretation
1	Comparison Of Two Lung Cancer Screening Scores Among Patients With Chronic Obstructive Pulmonary Disease A Community Study	Ane Aamli Gagnat, 2018	3	1	2	6	Good
2	Cancer development in patients with COPD a retrospective analysis of the National Health Insurance Service-National Sample Cohort in Korea	Song Voque, 2020	4	1	1	6	Good
3	Exploring The Impact Of Number And Type Of Comorbidities On The Risk Of Severe Copd Exacerbations In Korean Population: A Nationwide Cohort Study	Youngmee Kim, 2021	3	1	2	6	Good
4	Inhaled Corticosteroid Use And The Incidence Of Lung Cancer in COPD	Samy Suissa, 2019	3	1	2	6	Good
5	COPD and Lung Cancer Incidence In The Women's Health Initiative Observational Study: A Brief Report	Misako Nagasaka, 2020	3	1	2	6	Good
6	Influence of the Type of Emphysema in the Relationship Between COPD and Lung Cancer	Cecilia Mouronte-Robias, 2018	4	1	2	7	Good
7	Correlation between Lung Cancer and the HHIP polymorPHisms of Chronic Obstructive Pulmonary Disease (COPD) in the Chinese Han Population	Jing Xu, 2018	3	1	2	6	Good
8	Risk of Cancer After Lung Transplantation for COPD	Magnus Ekstrom, 2017	3	1	2	6	Good

9	Factors Associated with Lung Cancer in COPD Patients	Martin Sandelin, 2018	3	1	2	6	Good
10	Effect of COPD on Inflammation, Lymphoid Functions and Progression-Free Survival during First-Line Chemotherapy in Advanced Non-small Cell Lung Cancer	Marton Szentkereszty, 2019	3	1	2	6	Good
11	Spirometry Performed as Part of the Manchester Community-based Lung Cancer Screening Programme Detects a High Prevalence of Airflow Obstruction in Individuals Without a Prior Diagnosis of COPD	Haval Balata, 2020	4	1	2	7	Good
12	Chronic Obstructive Pulmonary Disease And Lung Cancer Incidence In Never Smokers: A Cohort Study	Hye Yun Park dkk, 2020	3	1	2	6	Good
13	The Incidence and Risk Analysis of Lung Cancer Development in Patients with Chronic Obstructive Pulmonary Disease: Possible Effectiveness of Annual CT-Screening	Hiroyoshi Machida dkk, 2021	4	1	2	7	Good
14	Statin Use and Lung Cancer Risk in Chronic Obstructive Pulmonary Disease Patients: A Population-Based Cohort Study	AJN Raymakers dkk, 2020	3	1	2	6	Good
15	Prevalence of Lung Cancer in Patients With Interstitial Lung Disease Is Higher than in Those with Chronic Obstructive Pulmonary Disease	Hye In Jung , 2018	4	1	2	7	Good
16	Risk Factors for Lung Cancer in COPD - Results from the Bergen COPD Cohort Study	Gunnar R, Husebo, 2019	3	1	2	6	Good

17	COPD-Dependent Effects of Genetic Variation in Key Inflammation Pathway Genes on Lung Cancer Risk	Donovan Watza, 2020	4	1	2	7	Good
18	Hospitalizations at the End of Life Among Chronic Obstructive Pulmonary Disease and Lung Cancer Patients: A Nationwide Study	Ana Rute Costa, 2021	3	1	2	6	Good
19	End-of-Life Health Care Utilization Between Chronic Obstructive Pulmonary Disease and Lung Cancer Patients	Luo-Ching Kuo, 2019	3	1	2	6	Good
20	Lung Cancer in Patients With Combined Pulmonary Fibrosis and Emphysema and Idiopathic Pulmonary Fibrosis. A Descriptive Study in a Spanish Series	Karina Portillo, 2017	4	1	2	7	Good
21	Prevalence of Comorbidities in COPD Patients by Disease Severity in A German Population	Timm Greulich, 2017	3	1	2	6	Good
22	Static Lung Hyperinflation Is an Independent Risk Factor for Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease	Ester Zamarron, 2021	4	1	2	7	Good
23	Impact of Chronic Obstructive Pulmonary Disease on Mortality: A Large National Cohort Study	Hye Yun Park , 2020	3	1	2	6	Good
24	Clinico-Epidemiological Characteristics of Men and Women With A New Diagnosis of Chronic Obstructive Pulmonary Disease: A Database (SIDIAP) Study	Josep Montserrat-Capdevila, 2021	3	1	2	6	Good

25	Risk Factors for Early Readmission after Acute Exacerbation of Chronic Obstructive Pulmonary Disease	Yong Suk Jo, 2020	3	1	2	6	Good
26	Statin Use and the Risk of Subsequent Hospitalized Exacerbations in COPD Patients with Frequent Exacerbations	Chieh-Mo Lin, 2020	4	1	2	7	Good
27	Low Uptake of Palliative Care For COPD Patients within Primary Care in The UK	Chloe I. Bloom, 2018	3	1	2	6	Good
28	Effect Of Multiple Comorbidities on Mortality in Chronic Obstructive Pulmonary Disease among Korean Population: A Nationwide Cohort Study	Youngmee Kim, 2021	3	1	2	6	Good
29	Radiologic Features of Precancerous Areas of the Lungs in Chronic Obstructive Pulmonary Disease	Shotaro Chubachi, 2017	4	1	2	7	Good
30	Predictors of Referral to Pulmonary Rehabilitation from UK Primary Care	Philip W Atone, 2020	3	1	2	6	Good
31	Comorbidities in Chronic Obstructive Pulmonary Disease: Results of A National Multicenter Research Project	Renata Rubinsztajn, 2018	3	1	2	6	Good
32	Real-World Retrospective Cohort Study ARCTIC Shows Burden of Comorbidities in Swedish COPD Versus Non-COPD Patients	Bjorn Stallberg, 2018	3	1	2	6	Good
33	Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) Comorbidities in Lithuanian National Database: A Cluster Analysis	Elena Jureviciene, 2022	4	1	2	7	Good
34	Comorbidities, Mortality, and Management of Chronic Obstructive Pulmonary Disease Patients Who	Hok Sum Chan, 2018	3	1	2	6	Good

	Required Admissions to Public Hospitals in Hong Kong - Computerized Data Collection and Analysis						
35	Histopathological Type of Lung Cancer and Underlying Driver Mutations in Patients with Chronic Obstructive Pulmonary Disease (COPD) versus Patients with Asthma and COPD Overlap: A Single-Center Retrospective Study	Tamami Sakai, 2020	4	1	2	7	Good