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Chronic obstructive pulmonary disease (COPD) complicating early-stage lung cancer (LC)

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No Relevant Disclosures

Three Main Points

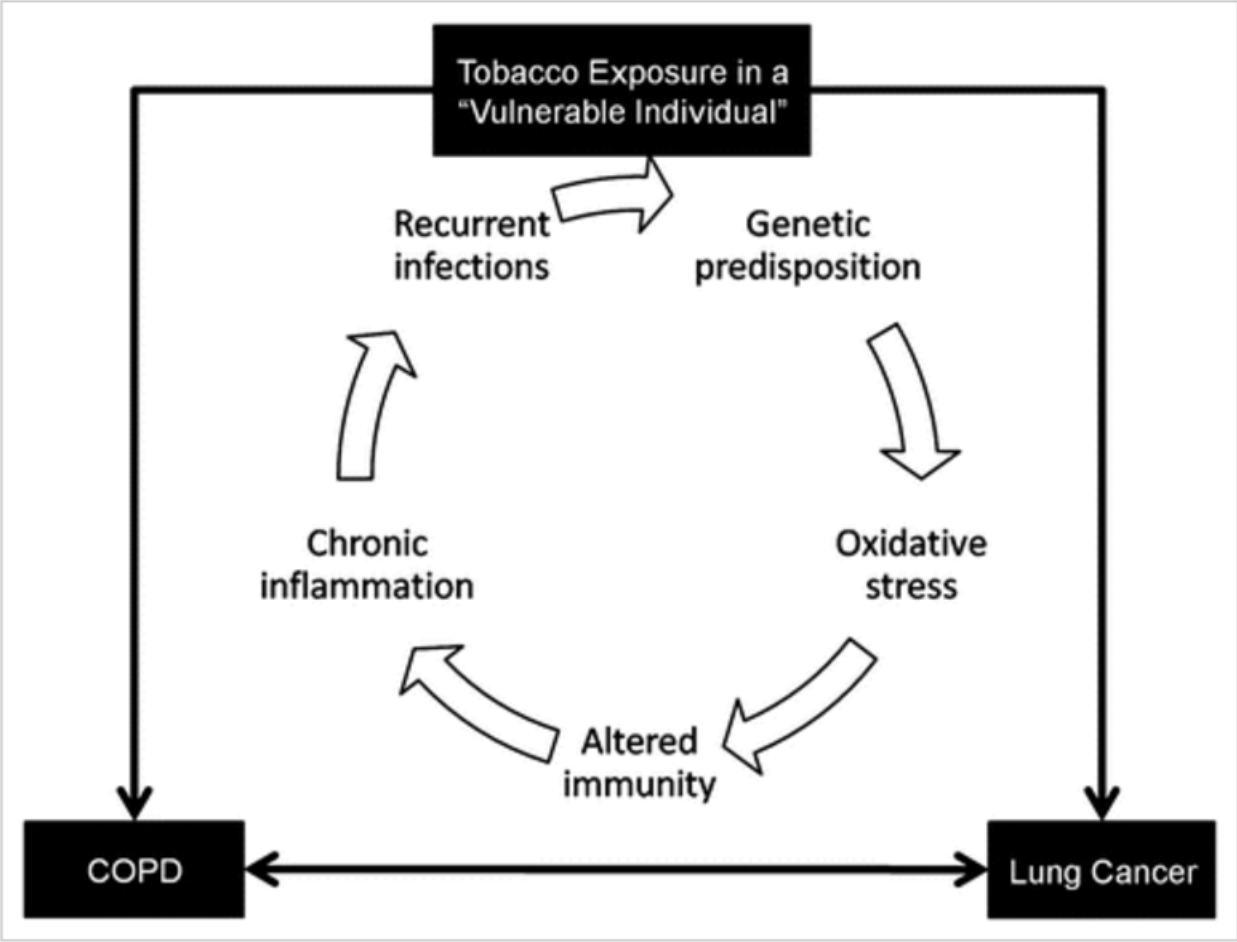
- **Overview: link between COPD and LC**
- **Prognosis of patients with COPD+LC**
- **Role of emphysema in LC outcome**

Link between COPD and LC

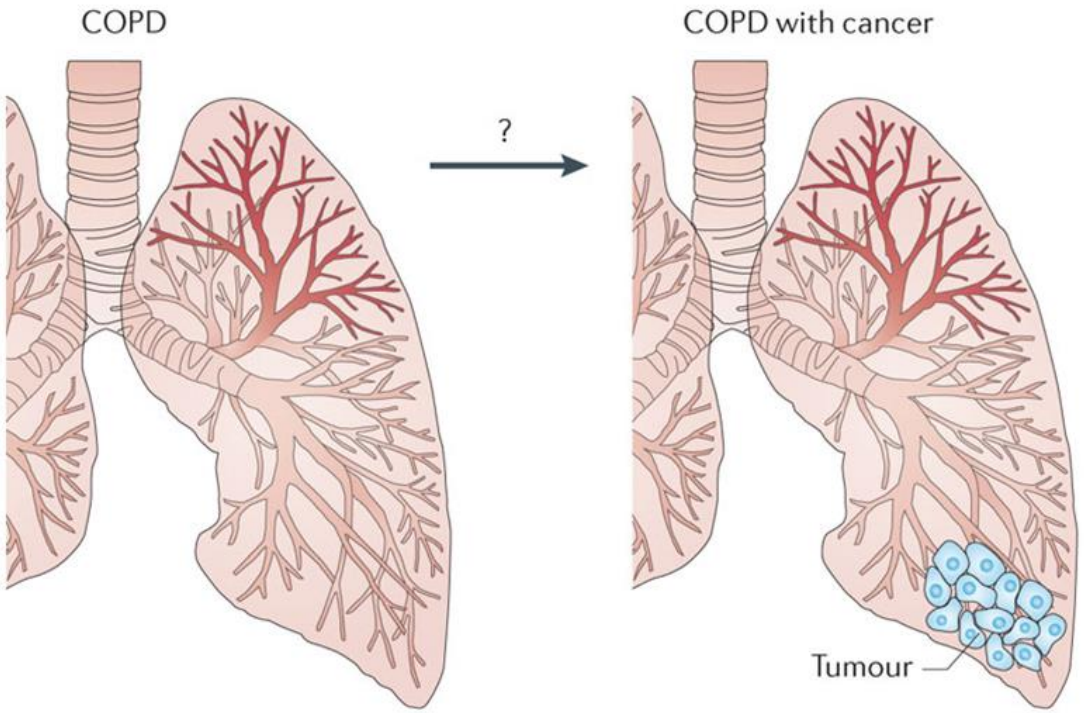
- **Time-tested observations**
- **Genomic and molecular mechanisms**
- **Clinical implications**

Mechanisms of association: COPD and LC

Raviv et al., Am J Resp & Critical Care; 2011



Candidate mechanisms linking COPD to LC



Genetics:
- Process oxidant or noxious stress
- EPHX, CYPs, MPO and NRF2

Cell cycle regulation:
- Avoid apoptosis
- Uncontrolled proliferation

Cytokines:
- NF-κB activation
- Regulate tumour microenvironment

Inflammation:
- Field propagation
- Cytotoxic versus growth promoting

Proteinases:
- Matrix degradation
- Release growth factors

Nature Reviews | Cancer

Studies linking COPD & LC

Study	Number of participants	Outcome	FEV_1 (% predicted)‡	Emphysema
Skilrud *et al.*[4]	226	Incidence	Cancers in 8.8% of cases (FEV_1 <70%) versus 2.0% of controls (FEV_1 >85%); $P = 0.024$	NA
Tockman *et al.*[5]	4,395	Mortality	• Cohort 1: RR 4.85 for FEV_1 <60% versus >60%; $P = 0.002$ • Cohort 2: RR 2.72 for FEV_1 60–85% versus >85%; $P = 0.043$	NA
Speizer *et al.*[7]	8,427	Mortality	Quartile-based FEV_1 analysis confers cancer risk (RR 2.0–8.27)	NA
Lange *et al.*[6]	13,946	Mortality	• RR 2.1 (95% CI 1.3–3.4) for FEV_1 40–79% versus >80% • RR 3.9 (95% CI 2.2–7.2) for FEV_1 <40% versus >80%	NA
de Torres *et al.*[19]	1,166	Incidence	RR 2.89 (95% CI 1.14–7.27) for FEV_1/FVC ratio <70% versus >70%	Semi-quantitative radiographic emphysema, RR 3.13 (95% CI 1.32–7.44)
Wilson *et al.*[17]	3,638	Incidence	OR 2.09 (95% CI 1.33–3.27) for any GOLD stage (FEV_1/FVC <70%)	Semi-quantitative radiographic emphysema, OR 3.56 (95% CI 2.21–5.73). After controlling for airflow obstruction, OR 3.14 (95% CI 1.91–5.15) for radiographic emphysema
Li *et al.*[20]	1,015	Incidence	NA	Semi-quantitative radiographic emphysema. Any = OR 2.79 (95% CI 2.05–3.81), >5% = 3.80 (95% CI 2.78–5.19), >10% = OR 3.33 (95% CI 2.30–4.82)
Zulueta *et al.*[21]	9,047	Mortality	NA	Semi-quantitative radiographic emphysema, HR 1.7 (95% CI 1.1–2.5); $P = 0.013$
Maldanado *et al.*[23]	1,520	Incidence	Cancer risk conferred by decreasing FEV_1, OR 1.15 (95% CI 1.00–1.32; $P = 0.046$); and FEV_1/FVC <70%, OR 1.29 (95% CI 1.02–1.62; $P = 0.0310$)	Automated volumetric determination of radiographic emphysema was not associated with lung cancer risk, OR 1.042 (95% CI, 0.816–1.329; $P = 0.743$)

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; NA, not applicable; OR, odds ratio; RR, relative risk. *All studies controlled for age and cigarette consumption. ‡The FEV_1 is reported as the percentage that would be predicted for that individual based on parameters that are known to influence the FEV_1, such as gender, age, height and race.

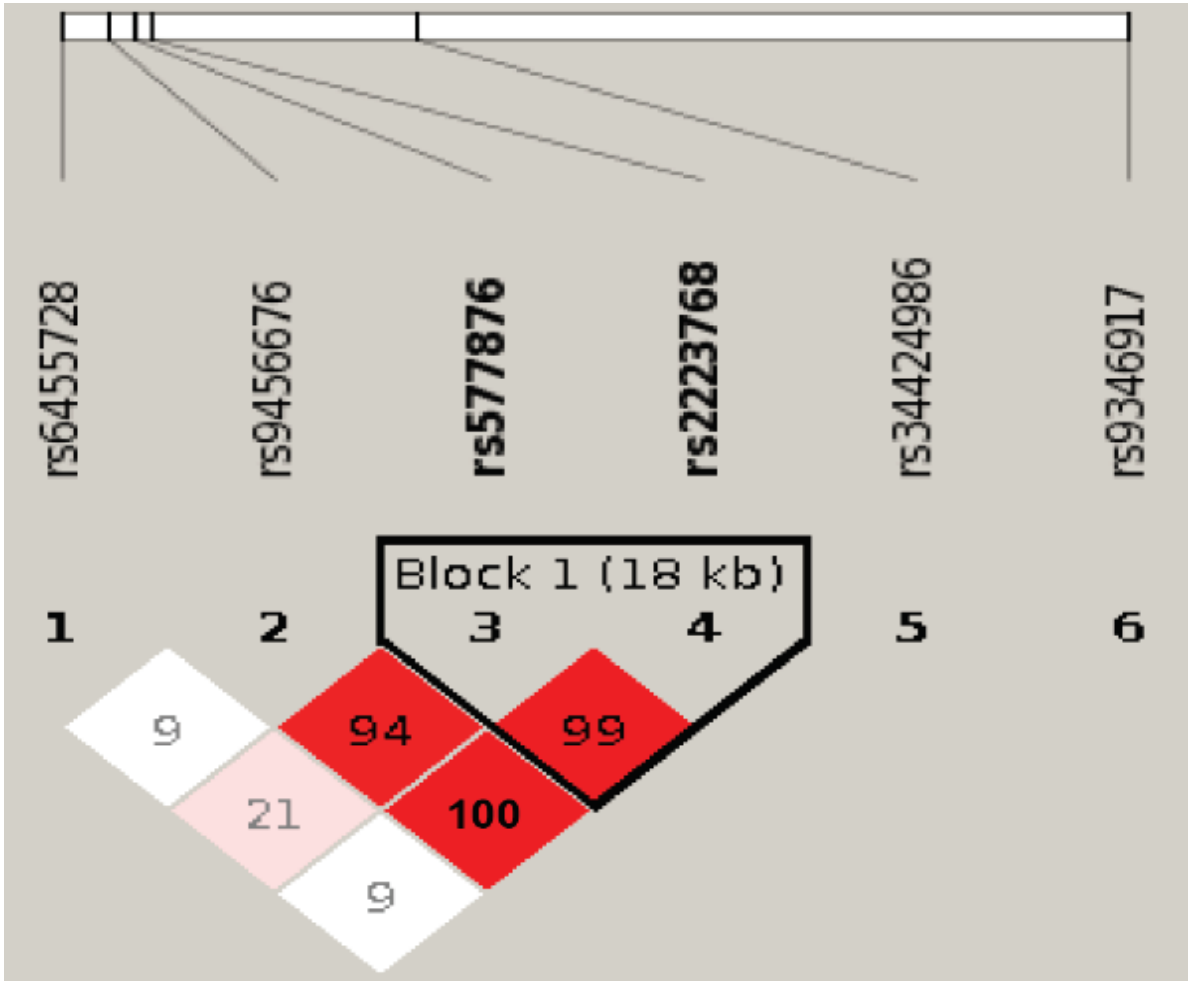
Houghton AM. Nature Rev Ca; 2013

Multiple-level validation identifies *PARK2* in the development of LC & COPD (Oncotarget 2016)

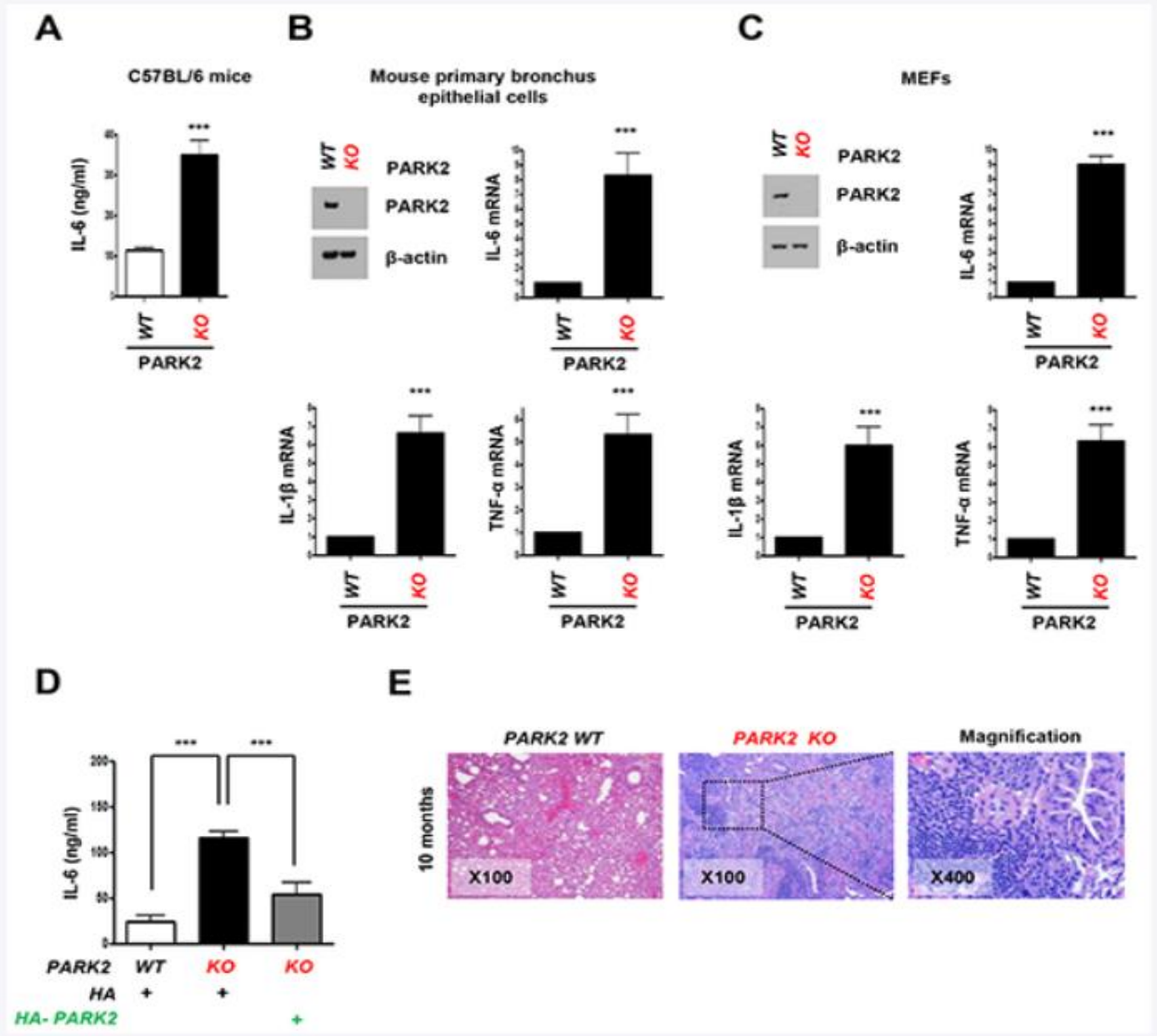
Table 1: Distribution of LC and COPD in 2484 cases and controls

	COPD +	COPD -	Total
LC +	n +/+ (573)	n +/− (612)	1185
LC −	n −/+ (537)	n −/− (762)	1299
Total	1110	1374	2484

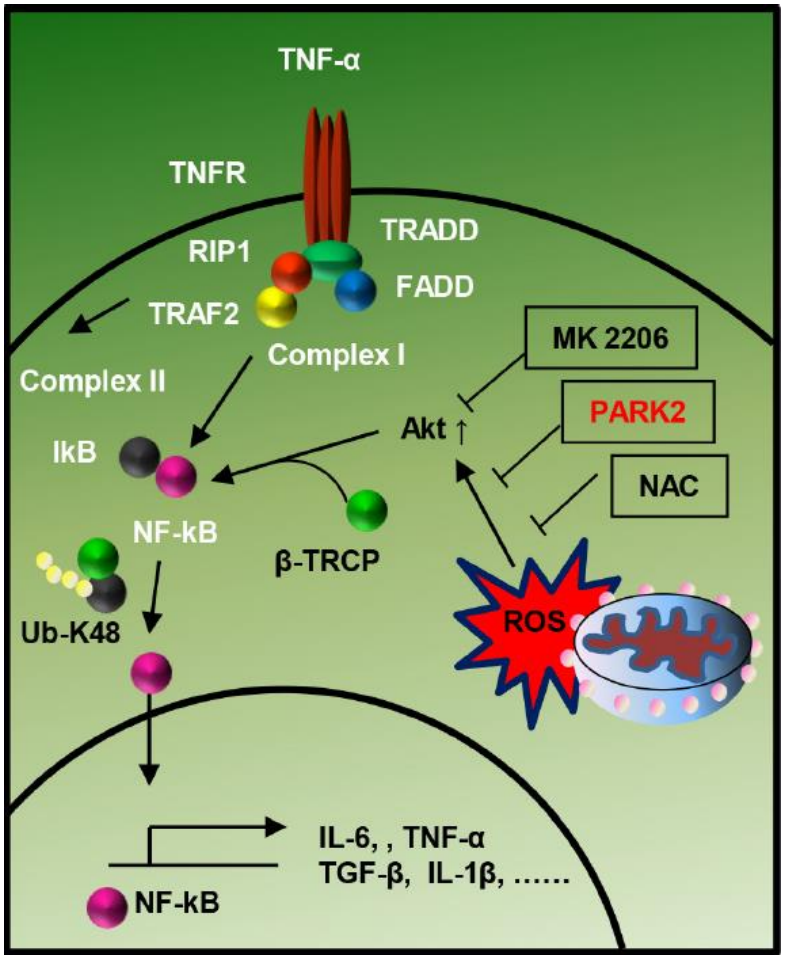
Multiple-level validation identifies *PARK2* in the development of LC & COPD (Oncotarget 2016)



Multiple-level validation identifies *PARK2* in the development of LC & COPD (Oncotarget 2016)



Schematic model

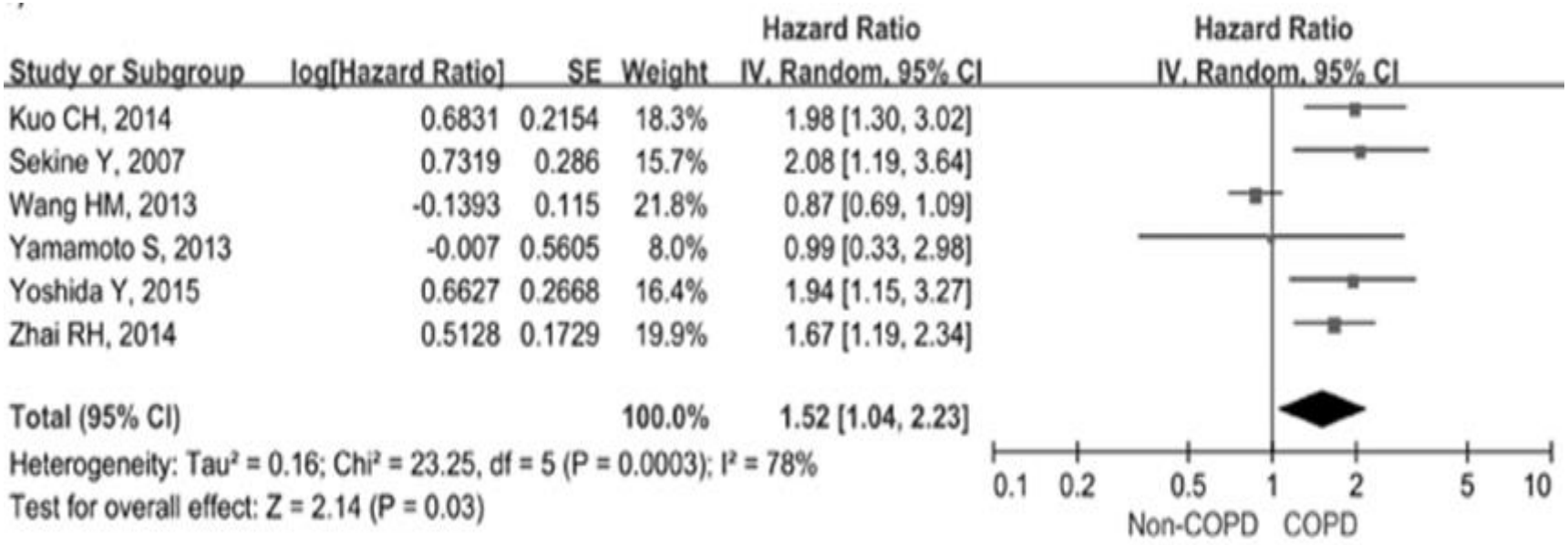


COPD & LC: Clinical Implications

- **Prognosis of patients with COPD+LC**
- **Role of Emphysema on LC patients' survival**
- **Regional emphysema score: a predictor of outcomes in early-stage lung cancer**

Prognosis of Patients with COPD+LC

- **Associations of concomitant COPD and LC survival** (*Gao et al., Respirology 2016*)**:**
  - **(a) Effect on disease-free survival (DFS)**
  - **(b) Effect on overall survival (OS)**



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Kuo CH, 2014	0.6831	0.2154	18.3%	1.98 [1.30, 3.02]
Sekine Y, 2007	0.7319	0.286	15.7%	2.08 [1.19, 3.64]
Wang HM, 2013	-0.1393	0.115	21.8%	0.87 [0.69, 1.09]
Yamamoto S, 2013	-0.007	0.5605	8.0%	0.99 [0.33, 2.98]
Yoshida Y, 2015	0.6627	0.2668	16.4%	1.94 [1.15, 3.27]
Zhai RH, 2014	0.5128	0.1729	19.9%	1.67 [1.19, 2.34]
Total (95% CI)			100.0%	1.52 [1.04, 2.23]

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 23.25$, df = 5 (P = 0.0003); $I^2 = 78\%$

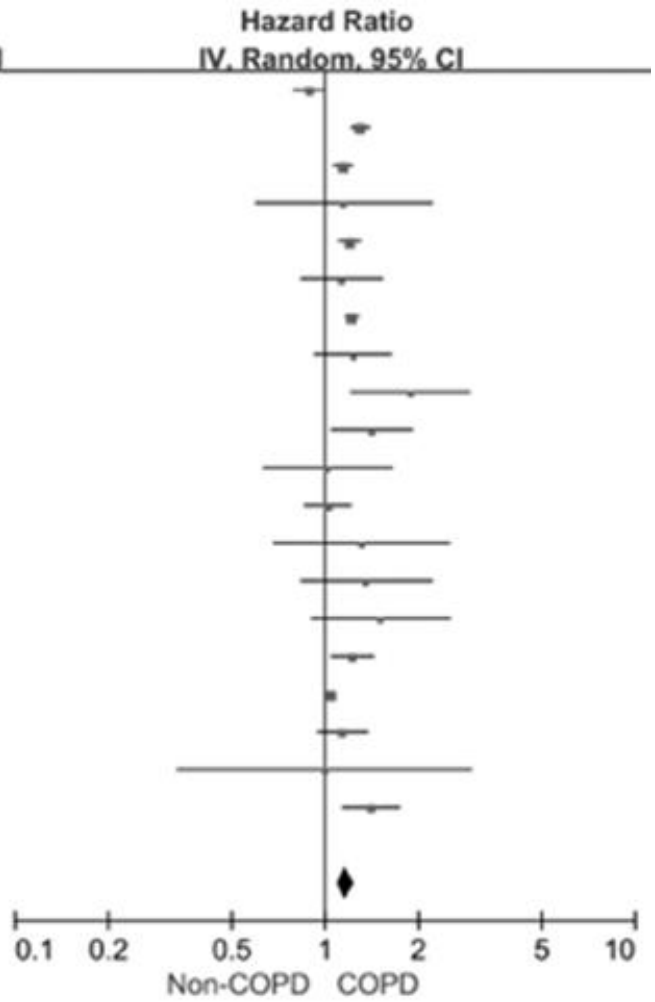
Test for overall effect: Z = 2.14 (P = 0.03)

Effect on overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Arca JA, 2009	-0.12	0.06	8.2%	0.89 [0.79, 1.00]
Birim O, 2006	0.2624	0.0378	9.7%	1.30 [1.21, 1.40]
Dy SM, 2006	0.131	0.0388	9.6%	1.14 [1.06, 1.23]
Gullón JA, 2011	0.1398	0.3379	0.9%	1.15 [0.59, 2.23]
Iachina M, 2014	0.1823	0.0447	9.3%	1.20 [1.10, 1.31]
Jian ZH, 2015	0.1222	0.1574	3.3%	1.13 [0.83, 1.54]
Kiri VA, 2010	0.2	0.03	10.1%	1.22 [1.15, 1.30]
Kondo R, 2011	0.207	0.1482	3.6%	1.23 [0.92, 1.64]
Kuo CH, 2014	0.6313	0.2281	1.8%	1.88 [1.20, 2.94]
Kurishima K, 2001	0.347	0.157	3.3%	1.41 [1.04, 1.92]
Lee SJ, 2014	0.0208	0.2468	1.6%	1.02 [0.63, 1.66]
López-Encuentra A, 2005	0.02	0.09	6.2%	1.02 [0.86, 1.22]
Mina N, 2012	0.27	0.3358	0.9%	1.31 [0.68, 2.53]
Sekine Y, 2002	0.3078	0.2521	1.6%	1.36 [0.83, 2.23]
Sekine Y, 2013	0.4121	0.2653	1.4%	1.51 [0.90, 2.54]
Tammemagi CM, 2003	0.2019	0.083	6.6%	1.22 [1.04, 1.44]
van de Schans SA, 2007	0.0392	0.0193	10.6%	1.04 [1.00, 1.08]
Wang HM, 2013	0.131	0.0975	5.8%	1.14 [0.94, 1.38]
Yamamoto S, 2013	-0.007	0.5605	0.4%	0.99 [0.33, 2.98]
Zhai RH, 2014	0.3409	0.1116	5.0%	1.41 [1.13, 1.75]
Total (95% CI)			**100.0%**	**1.17 [1.10, 1.25]**

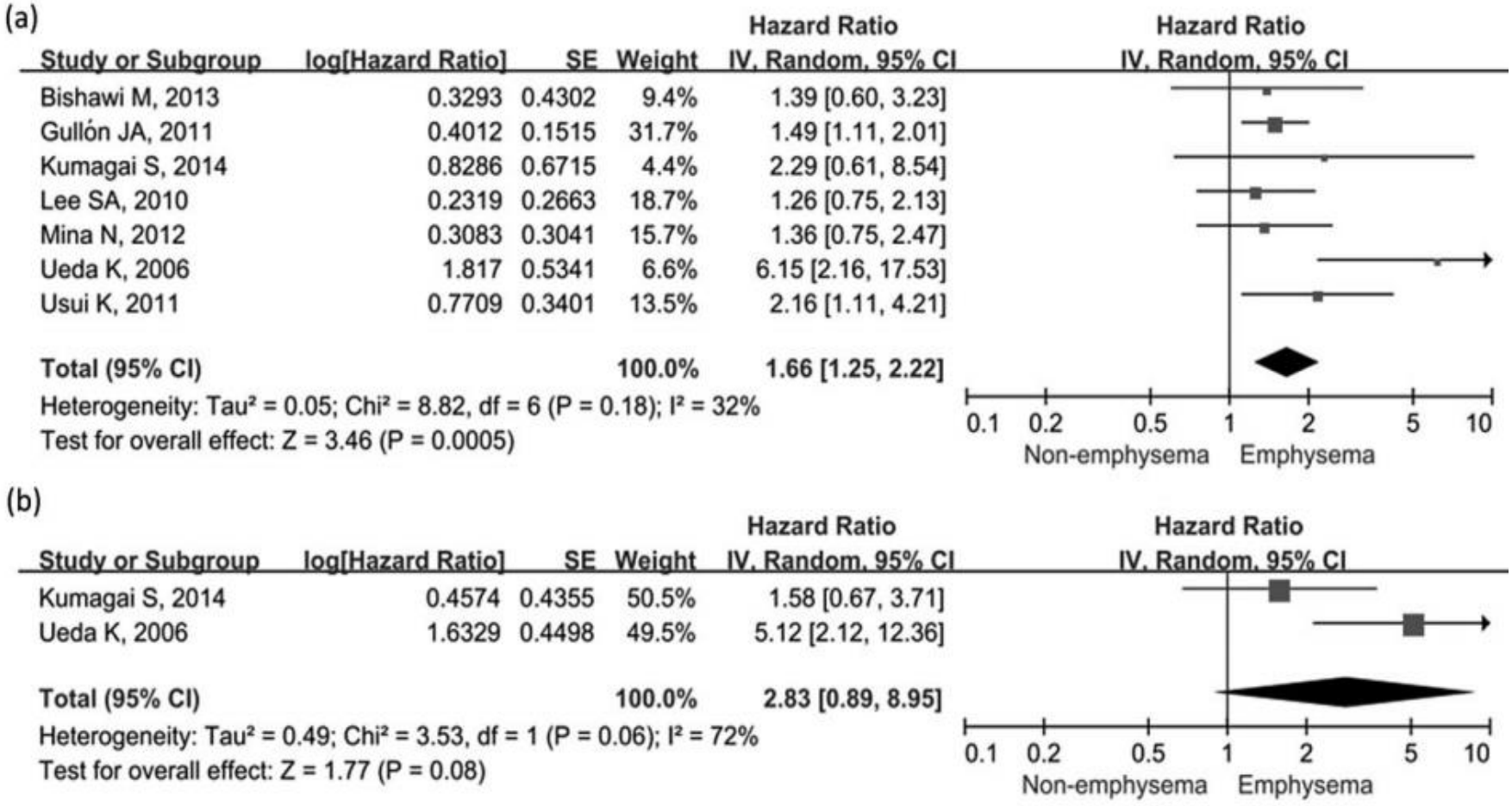
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 72.62$, df = 19 ($P < 0.00001$); $I^2 = 74\%$

Test for overall effect: $Z = 4.66$ ($P < 0.00001$)



Gao et al., Respirology 2016

The Role of Emphysema: OS vs. DFS



Gao et al., Respirology 2016

Regional emphysema score: a predictor of outcomes in early-stage lung cancer

Jie Dai1,2, Ming Liu1,2, Stephen J. Swensen3, Shawn M. Stoddard2, Jason A. Wampfler4, Andrew H. Limper5, Gening Jiang1, Ping Yang2

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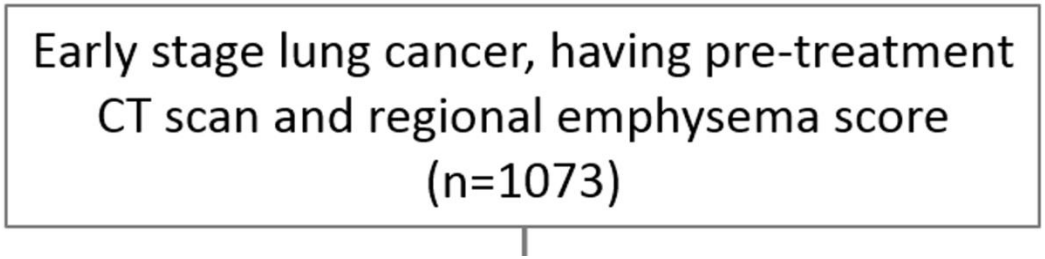
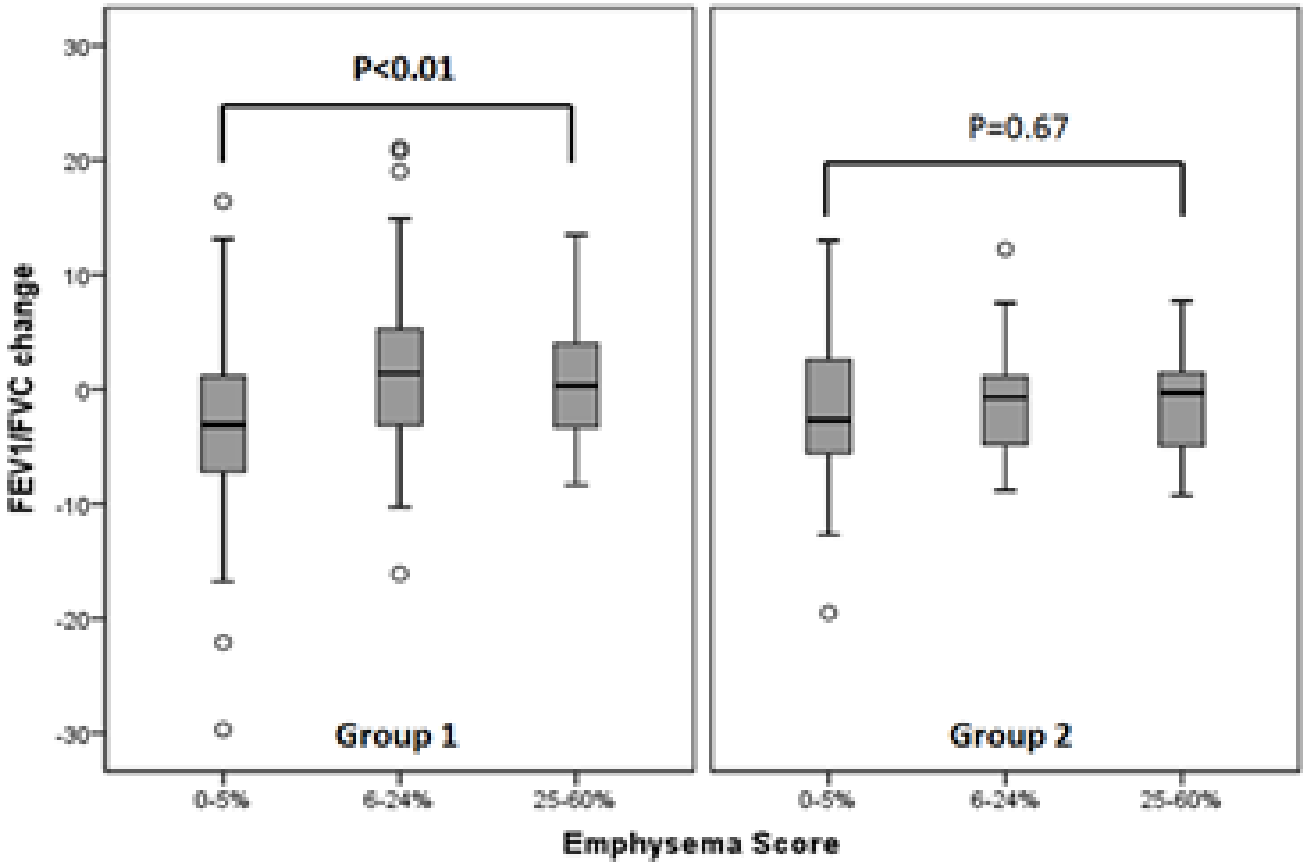
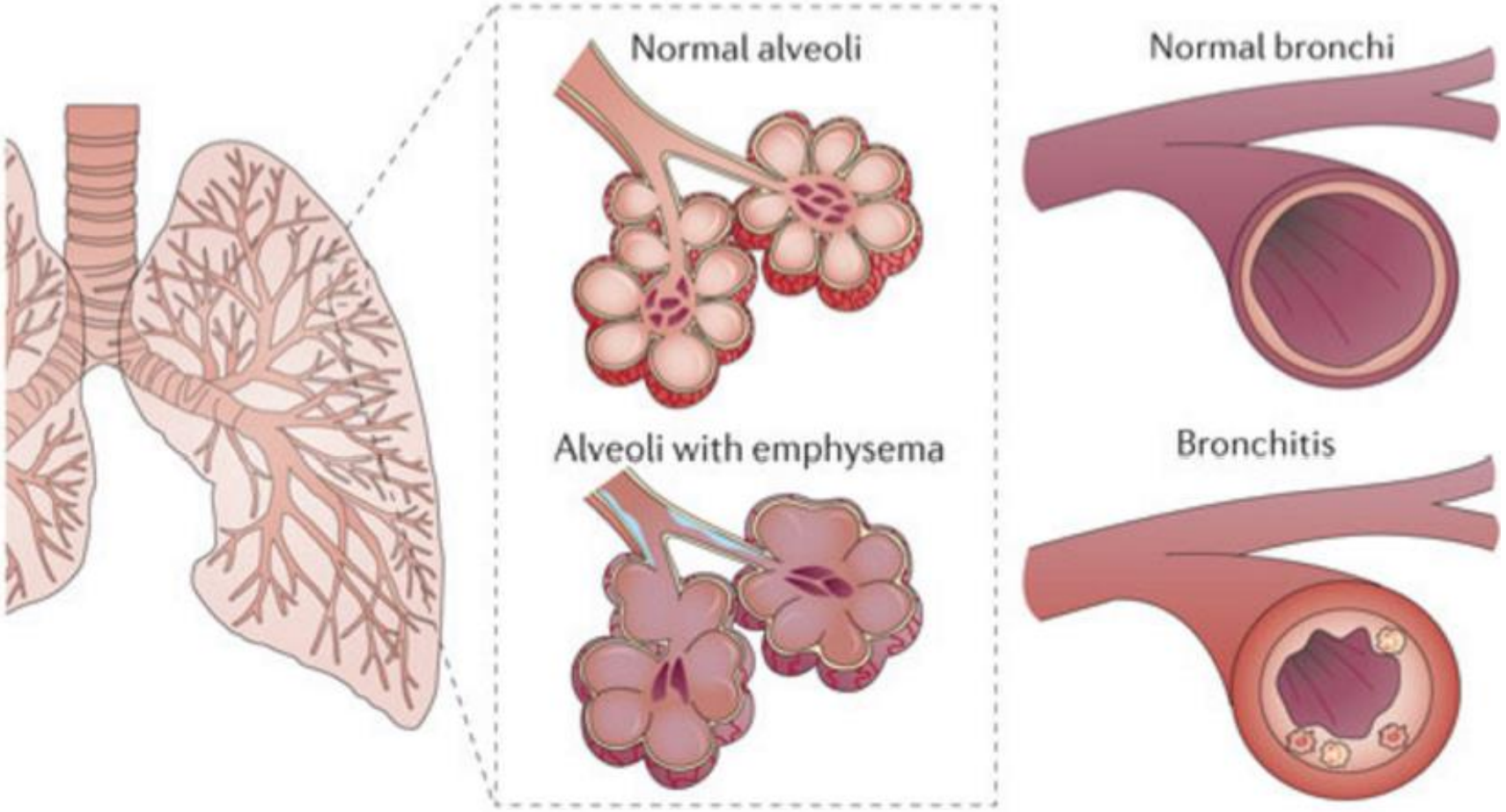
Study Population



Postoperative pulmonary function changes <2 years



- Classically, COPD subdivided into chronic bronchitis & emphysema
- Most commonly but not always, patients exhibit both



Three Take-home Messages

- **Mechanisms from COPD progressed to LC**
- **Prognosis of patients with COPD ± LC**
- **Regional emphysema score: a predictor of outcomes in early-stage lung cancer**