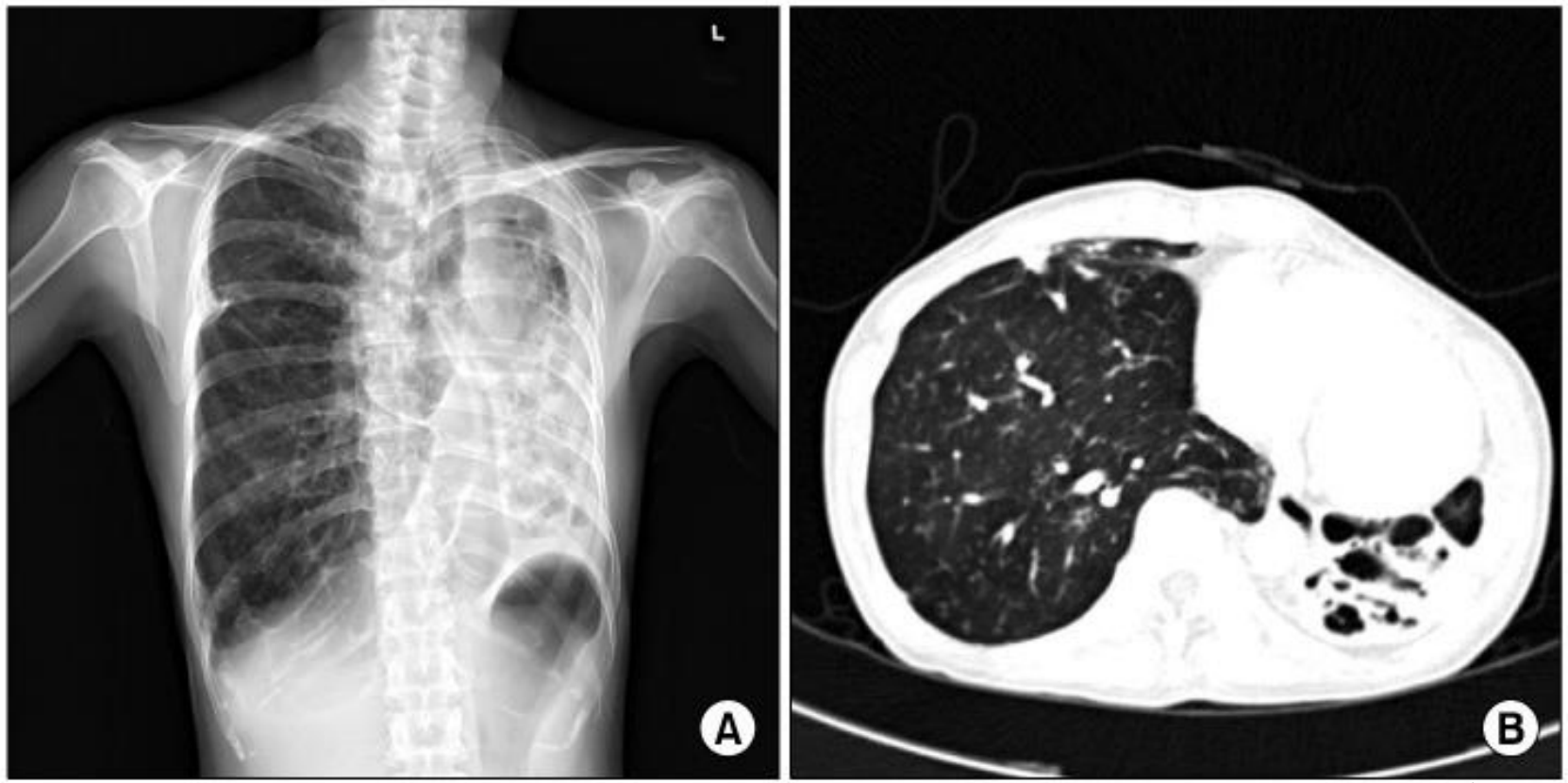
Lung Health Study



Korea Med Synapse

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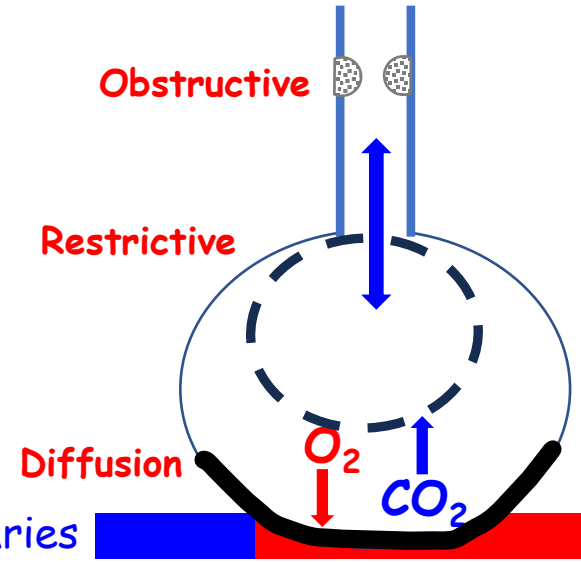
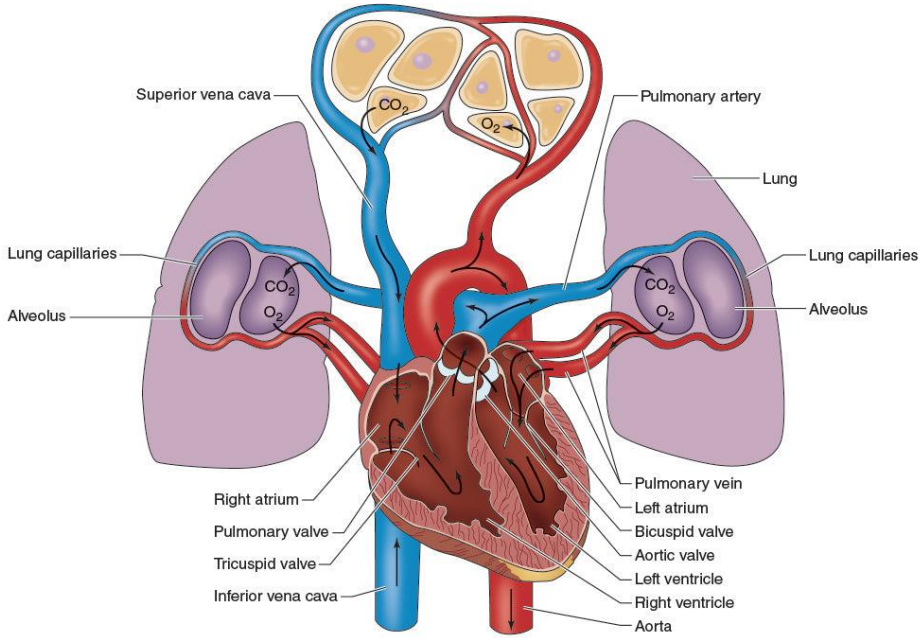
What Lungs Do

- Ventilation
- Perfusion
- Gas exchange





VC → RA → RV → PA → alveolar capillaries pulmonary veins → LA → LV → aorta

Long TB

Estimated 155M TB survivors alive in 2020 (Dodd, *Lancet Infect Dis* 2021)

- Pooled standardized mortality ratio for TB survivors 2.9 vs people without TB (Romonowski, Lancet Infect Dis 2019)
- Lifetime burden of disease after TB (Menzies, *Lancet Glob Health* 2021)
  - Estimated 98-151M DALYs due to incident TB
  - 12.1 DALYs per incident case, with 6.3 from disease episode and 5.8 from post-TB sequelae
  - Greatest burden in younger people from high TB incidence countries
- Cardiovascular disease
  - Taiwan NHIRD: aHR 1.40 for ACS overall, 6.58 for age 41-64, and 10.20 for age ≥65 (Chung, *IJTLD* 2014)
- Lung cancer
  - aHR 1.72 in 4.8 yrs overall; aHR 6.78 in 20 pack-yr smokers (Moon, *Clin Infect Dis* 2023)
- Autoimmunity?

Post-TB Lung Disease

Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to prior TB
- 1st International Post-Tuberculosis Symposium, 2020

- PTLD prevalence reported in 18-87% of survivors across multiple studies (median > 50%)
- Obstructive, restrictive, and mixed ventilatory defects in various proportions
- Worse function with DR-TB
- Worse function with smoking history
- Worse function in rural vs urban settings in some studies
- Median values improve over time during and after treatment
- Prior TB significantly associated with COPD diagnosis (OR=3.05) (Byrne, Int J Infect Dis 2021)
    - Strongest association in high TB burden countries, never smokers, younger people

Recent examples: Taylor, *eClinicalMedicine*, 2023; and Ivanova, *Eur Respir Rev*, 2023

Mechanisms & Manifestations

- Collateral damage from immune response
- Matrix digestion, epithelial injury, bronchiolitis, pleuritis
- Fibrotic resolution benefited hosts before antibiotics
- Multiple cell types & pathways involved

- Pathologies
  - Pneumonitis
  - Cavitation
  - Bronchiolitis

  } Acute phase

  - Parenchymal fibrosis
  - Bronchiectasis
  - Pleural & pericardial fibrosis

  } Resolution

- Late sequelae
  - COPD
  - Restrictive ventilatory defect
  - Aspergilloma
  - Exacerbations of bronchiectasis
  - Pulmonary hypertension

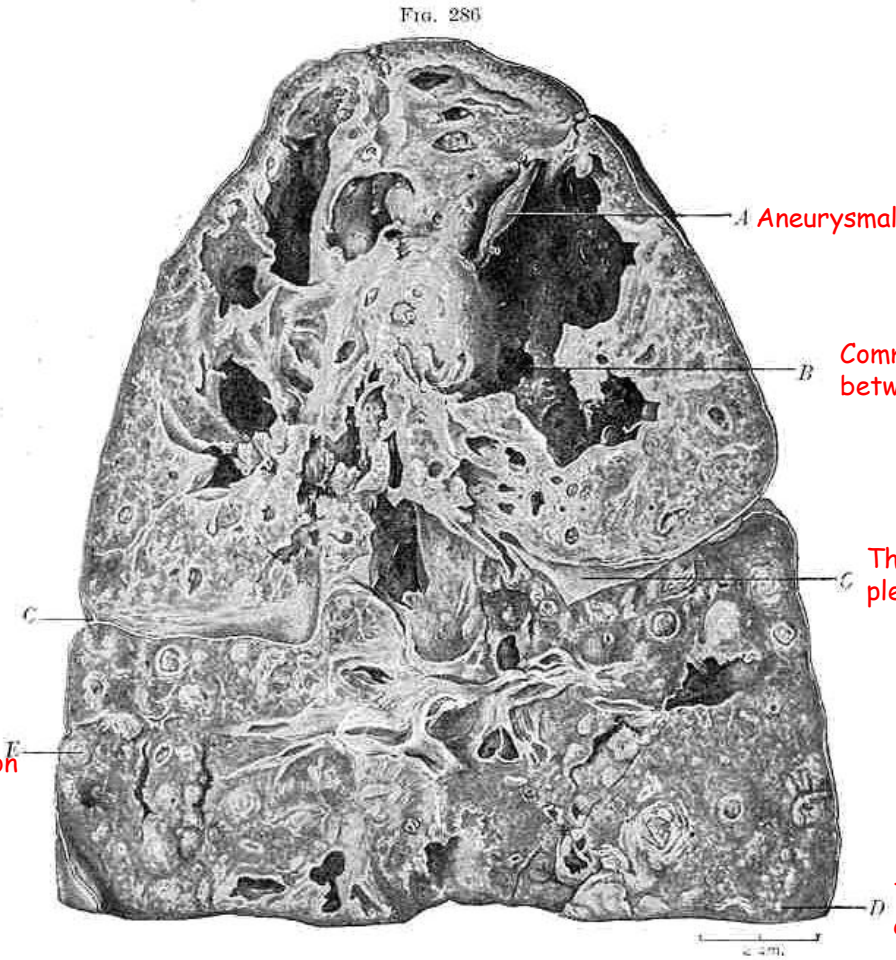


FIG. 286

Left lung, superior lobe, and upper part of lower lobe, the former containing a number of communicating caverns, brought about by tuberculous infiltration, caseation, and evacuation of the contents through the bronchi: *A*, aneurysmal dilatation of an artery spanning one margin of a large cavity; *B*, communication with another cavity; *C*, *C*, thickened and adherent pleura between the two involved lobes. The pleura over both lobes is thickened, and at the autopsy the cavity had been obliterated by universal adhesion; *D*, a small group of tubercles in which caseation is just beginning; *E*, a fused group of tubercles, farther advanced that at *D*. (Hare.)

Adami & McRea, 1914

Gaps

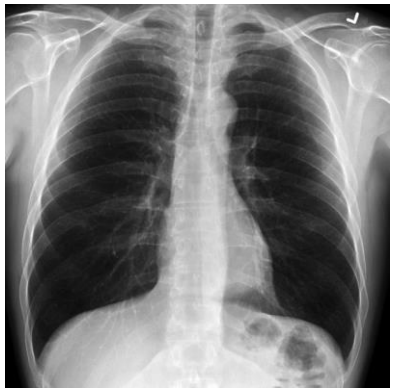
- Plethora of studies with **small cohorts** at one or **few sites**
- Limited assessment of clinical & demographic PTLD **risk associations**
- Very limited assessment of **pediatric PTLD**
- Studies limited to short **timespan** post-TB
- Limited **mechanistic studies**
  - Roles for neutrophils, NETs, inflammatory macrophages, T cells, fibrocytes & MMT, metalloproteinases, TGFb, pro-resolving mediators
  - *Mtb* genotype associations?
- Criteria for interventional trial participant selection

What to Measure

Parameter	Pros	Cons
Peak flow	Simple and inexpensive	Effort-dependent Limited information
Spirometry	Fundamental PFT data Standardized, $$	Effort-dependent Transmission risk
Lung volumes	Accurate diagnosis of restrictive defects, $$$	Requires a body box Transmission risk
DLCO	Accurate diagnosis of diffusion defects, $$	Effort-dependent Transmission risk
Exercise (±oximetry)	Simple and inexpensive Cardiovascular function	Low sensitivity for mild impairment
QoL instruments	Simple and inexpensive	Administration time, nonspecific
CXR, CT, PET	Structural correlate $, $$, $$$, respectively	You get what you pay for Radiation, glucose

Why measure lung health?

Pre-TB



Active TB

Collateral damage

Healed TB

Resolution

Demographics
Behaviors
Genetics

Prediction

Max damage at presentation
Anti-inflammatory drugs
Metalloproteinase inhibitors
Anti-fibrotic drugs

Treatment

Smoking cessation?
Bronchodilators?
Pulmonary rehab?
Supplemental oxygen?

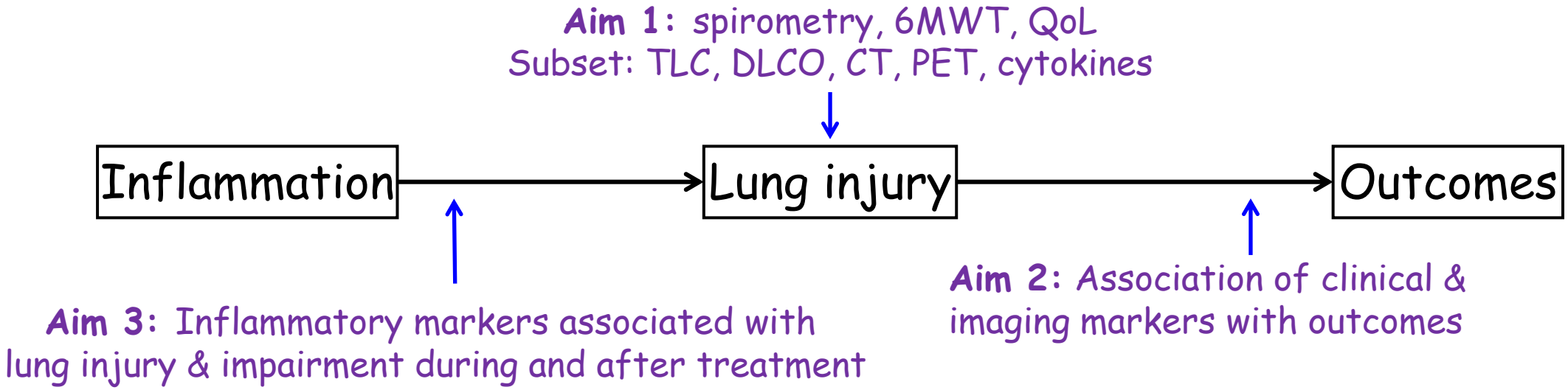
Management

RePORT India Aim 3

DJ Christopher & Akshay Gupte

1. Functional & morphological phenotypes of ATLD & PTLD.
2. Association between lung injury markers & treatment outcomes
3. Plasma & sputum inflammatory markers of lung injury & PTLD

Prospective cohort study at 5 sites
Adults with DS-TB and no prior TB or chronic lung disease
325 participants evaluated for 18 months (M0, 2, 6, 12, 18)



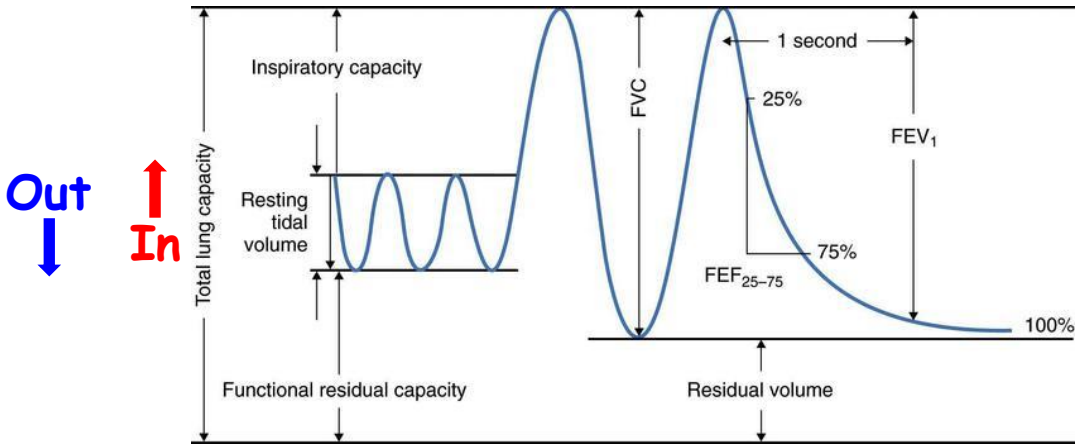
Why they call it re-search

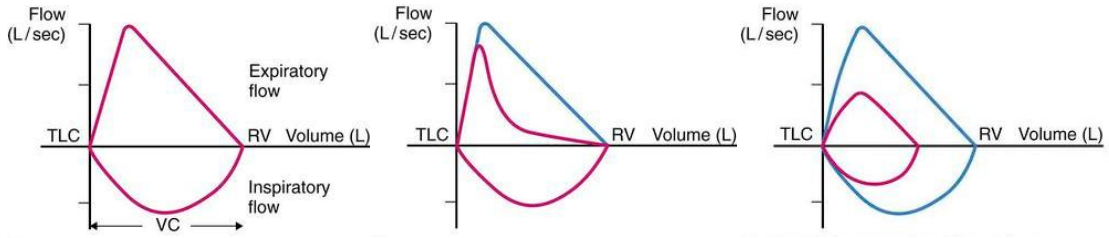
Lincoln NS, Bosworth EB, Alling DW. The after-history of pulmonary tuberculosis. III. Minimal tuberculosis. *Am Rev Tuberc* 1954; 70:15-31.

Alling DW, Lincoln NS, Bosworth EB. The after-history of pulmonary tuberculosis. V. Moderately advanced tuberculosis. *Am Rev Tuberc* 1954; 70:995-1008.

Alling DW, Bosworth EB, Lincoln NS. The after-history of pulmonary tuberculosis. IV. Far advanced tuberculosis. *Am Rev Tuberc* 1955; 71:519-528.

How to measure (spirometry)





Normal **Obstructive** **Restrictive**

- Low FEV1/FVC ratio = obstructive ventilatory defect
- Low FEV1 & FVC suggests restrictive ventilatory defect
- % predicted values correct for age, sex, race, and height
- 10% change is clinically significant
- PRISm (FEV1/FVC ≥0.70 with FEV1 <80% predicted)

<u>Subjective measures</u>

- QoL instruments (St. George's, CAT)
- MRC dyspnea scale

ACS risk/time

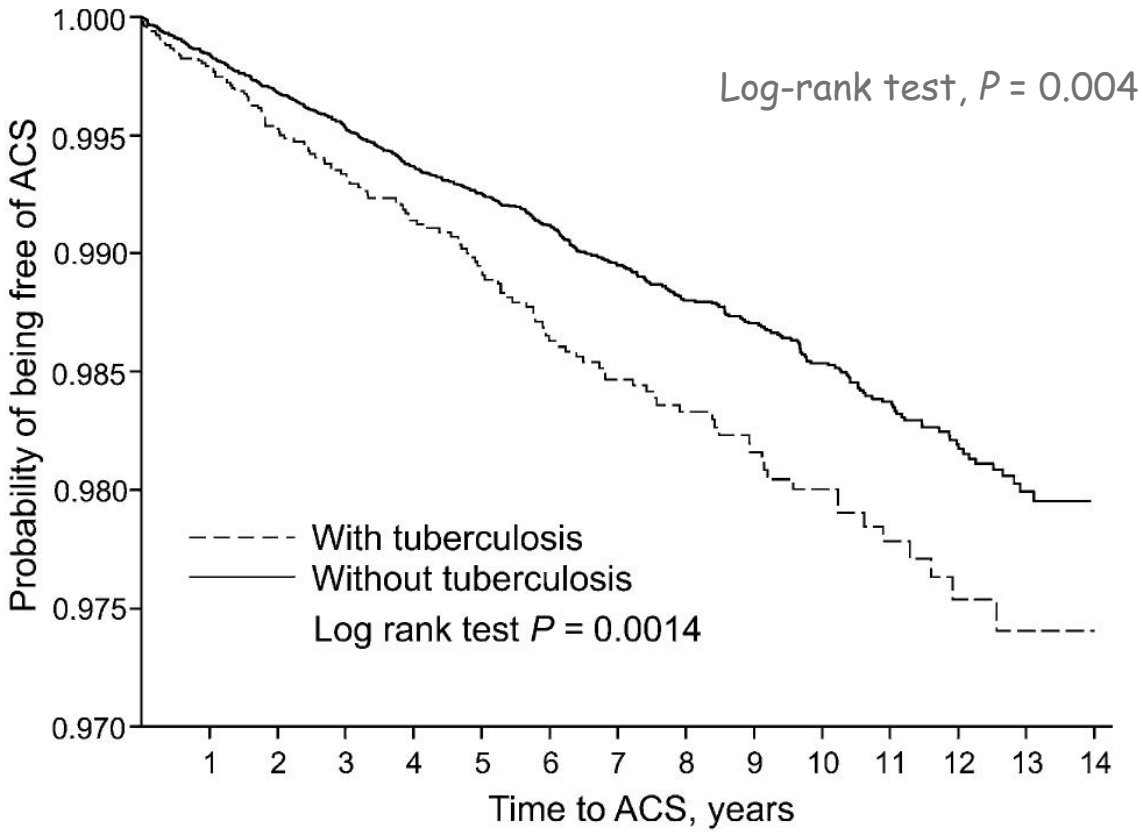


Figure Probability of being free of ACS development for patients with (dashed line) or without (solid line) tuberculosis. ACS = acute coronary syndrome.

Chung, *Int J Tuberc Lung Dis* 2014