結核癒後之慢性肺部感染症

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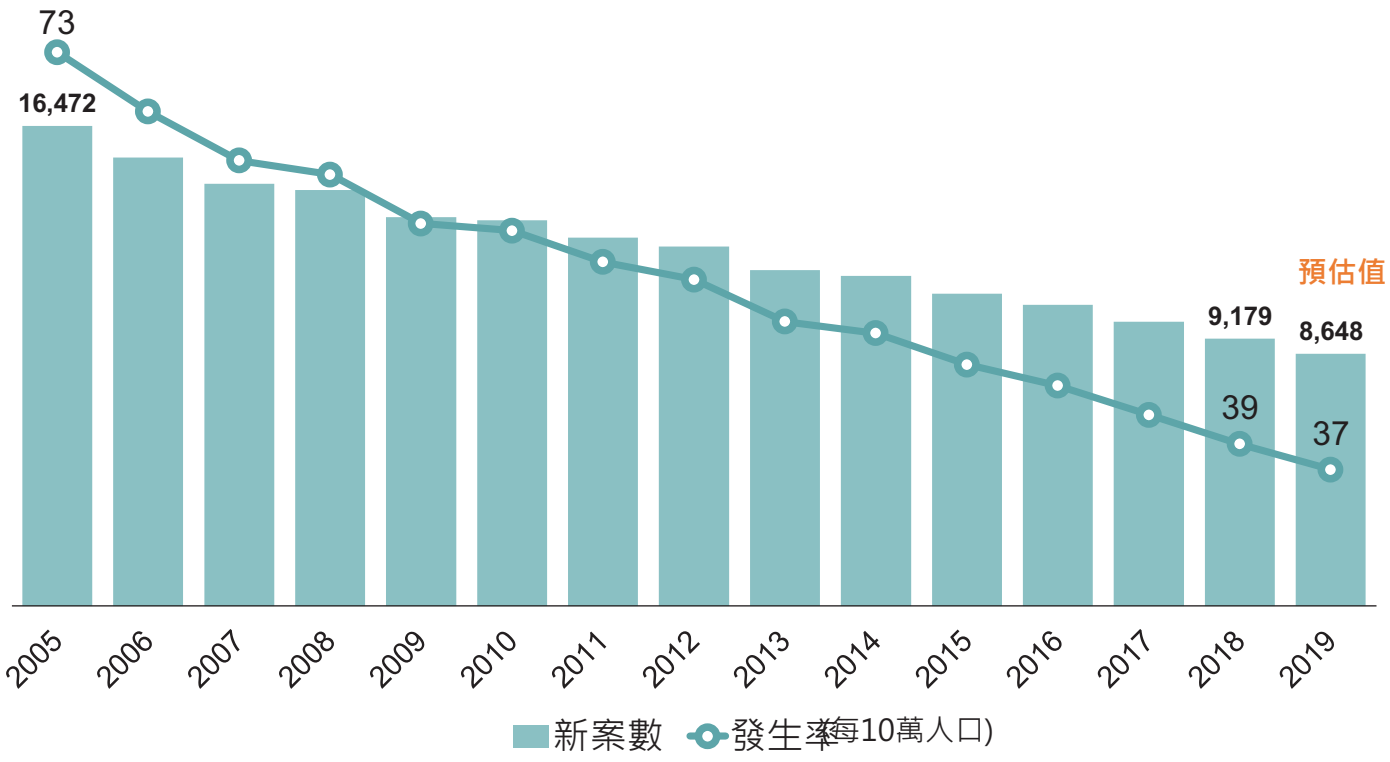
內 容 大 綱

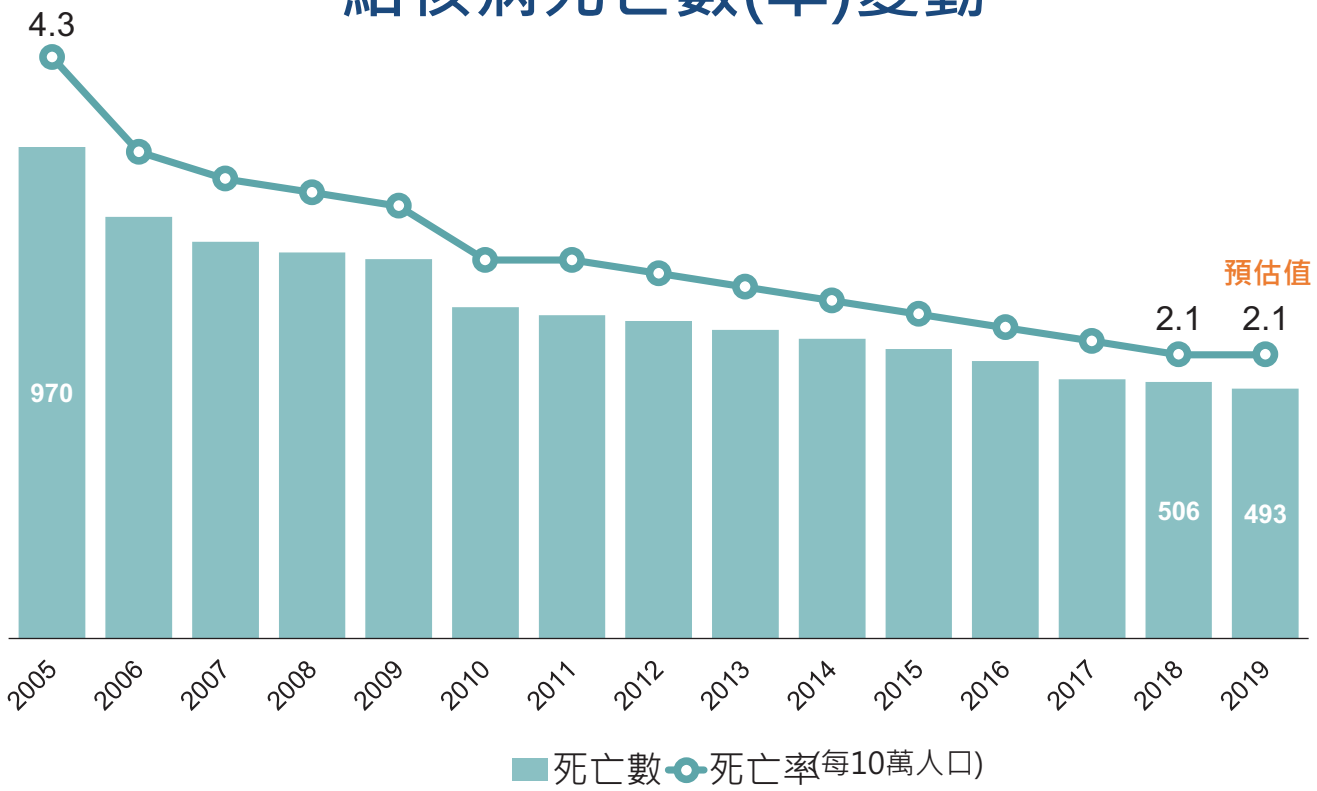
- 肺結核患者癒後之樣貌與後遺症
- 慢性肺部麴菌感染症與陳舊性結核
- 非結核分枝桿菌感染症與陳舊性結核
- 總結

肺結核患者癒後之樣貌與後遺症

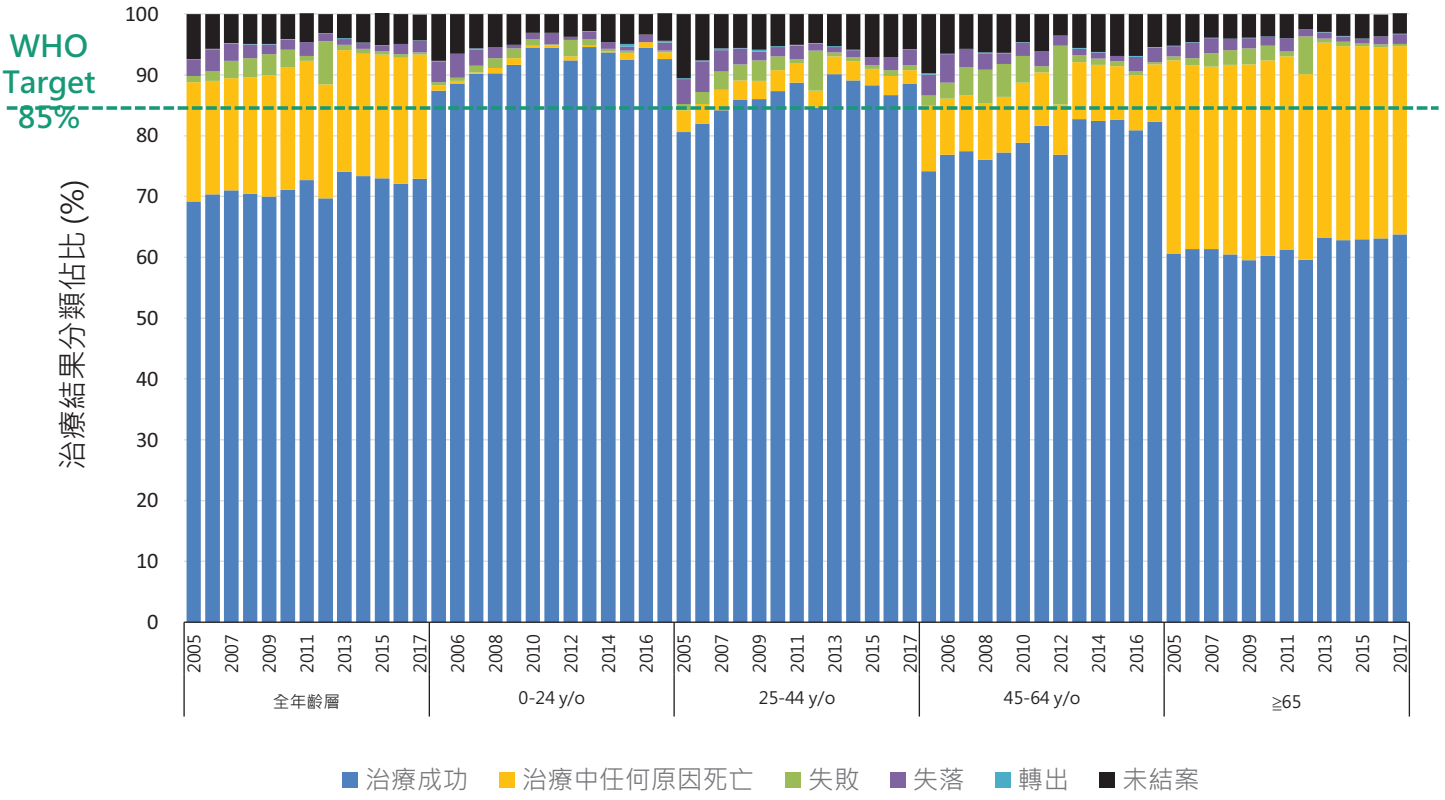
全國結核病發生率



結核病死亡數(率)變動



結核病12個月治療追蹤結果



What About Post-TB Care and Follow-up

完成治療後的監測：目前的證據顯示，完成治療後的結核病人，比一般人有更高的機會再得結核病。完治後的第一年建議每半年追蹤一次，此後每年追蹤一次。追蹤時，建議安排胸部X光檢查，並考慮驗痰。

Long Shadow of TB

FIRST INTERNATIONAL
POST TUBERCULOSIS SYMPOSIUM 2019
STELLENBOSCH, SOUTH AFRICA

Comment › Lancet Infect Dis. 2019 Nov;19(11):1170-1171. doi: 10.1016/S1473-3099(19)30564-X.

The Long Shadow Post-Tuberculosis

Brian Allwood [1], Marieke van der Zalm [2], Goodman Makanda [3], Kevin Mortimer [4], Steering Committee of the First International Post-Tuberculosis Symposium

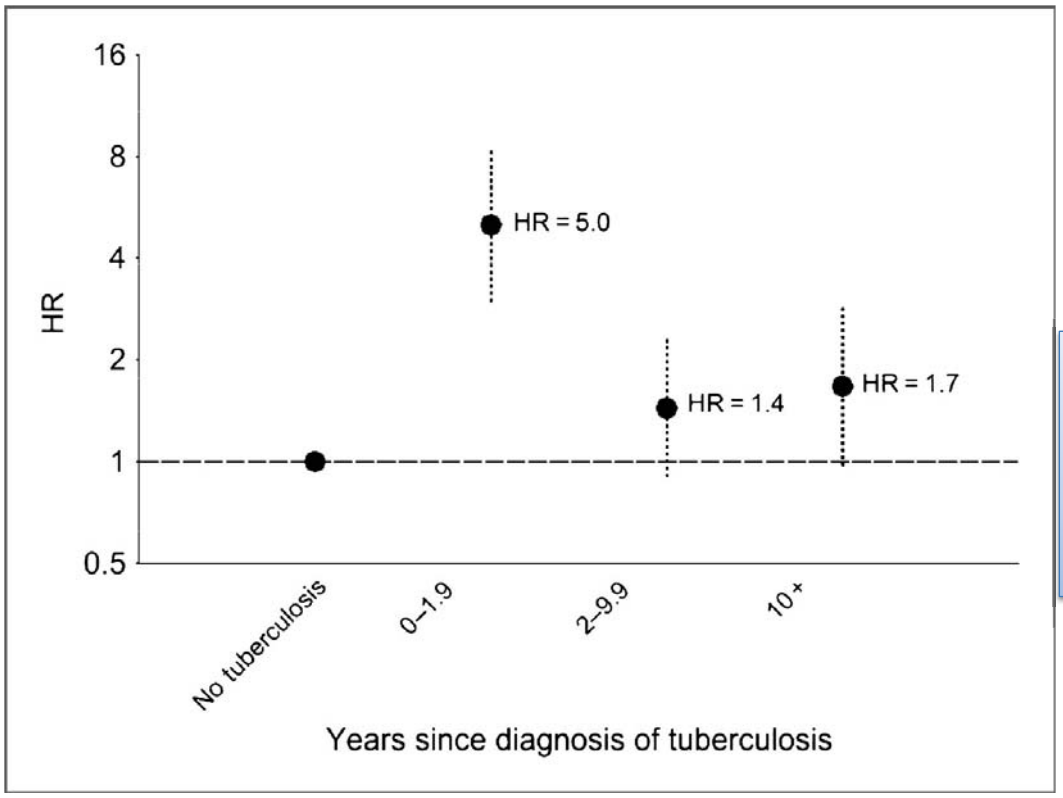
Collaborators, Affiliations + expand

PMID: 31657778 DOI: 10.1016/S1473-3099(19)30564-X

Table 1 Evidence map of the number of research articles that addressed post-tuberculosis (TB) chronic lung disorders by main outcome and post-TB conditions under study

	Main study outcome										
Post-TB conditions	Prevalence	Proportion	Predictors	Comorbidities/ complications	Progression	Surgery	Ventilation	Rehabilitation	Medication	Prevention	Total
TB sequelae (unspecified)	0	3	1	10	7	16	11	5	1	0	54
Aspergillosis	7	1	0	0	1	4	0	0	0	0	13
Bronchiectasis	0	3	0	2	1	1	1	0	0	0	8
Bronchial stenosis	0	0	0	0	0	9	0	0	0	0	9
Haemoptysis	0	0	0	0	0	5	0	0	0	0	5
Other (specified)*	0	2	2	6	1	0	0	0	1	0	12
Obstructive disorder	4	10	4	1	3	0	0	0	1	0	23
Pulmonary impairment	2	15	8	1	2	0	1	0	0	0	29
Chest X-ray abnormalities	1	7	1	1	0	0	0	0	0	0	10
Respiratory symptoms	1	9	0	0	0	0	0	0	0	0	10
Total	13	39	16	21	15	35	13	5	3	0	156

For each included article, a single main study outcome and all post-TB conditions under study are listed. See online supplementary file 3 for definitions of study outcomes.
*Other: pulmonary hypertension, emphysema, fibrosis, asthma.



Lung cancer risk remains elevated after TB treatment

Shiels et al. Cancer Epidemiol Biomarkers Prev 2011

Post-TB CT findings and patterns

	Country	n	Cavitation	Bronchiectasis	Fibrosis	Nodules
Poey et al. 1997	Martinique	27	7.4%	85.2%	92.6%	48%
Long et al. 1998	Canada	20	Not mentioned	50%	80%	55%
Bombarda et al. 2003	Brazil	20	30%	35%	70%	55%
Lee et al.2008	Taiwan	52	34.6%	44.2%	92.3%	55.8%
Rufino et al. 2015	Brazil	74	16%	86%	Not mentioned	48%

Meghji J et al. Plos One 2016

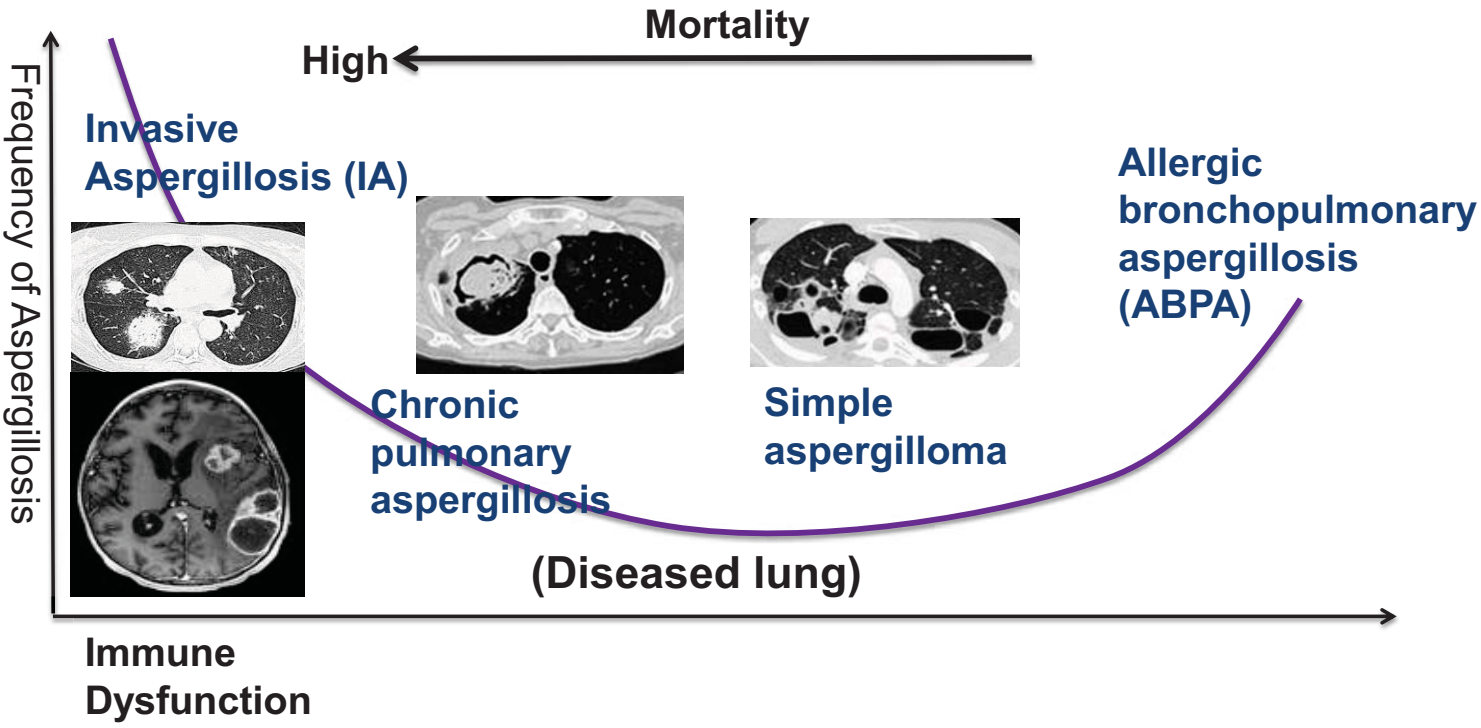
Post-TB Infectious Treatment Complications

- **Acute**- virus (influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19)), bacterial pneumonia

- **Chronic**- Chronic pulmonary aspergillosis (CPA), nontuberculous mycobacteria (NTM)

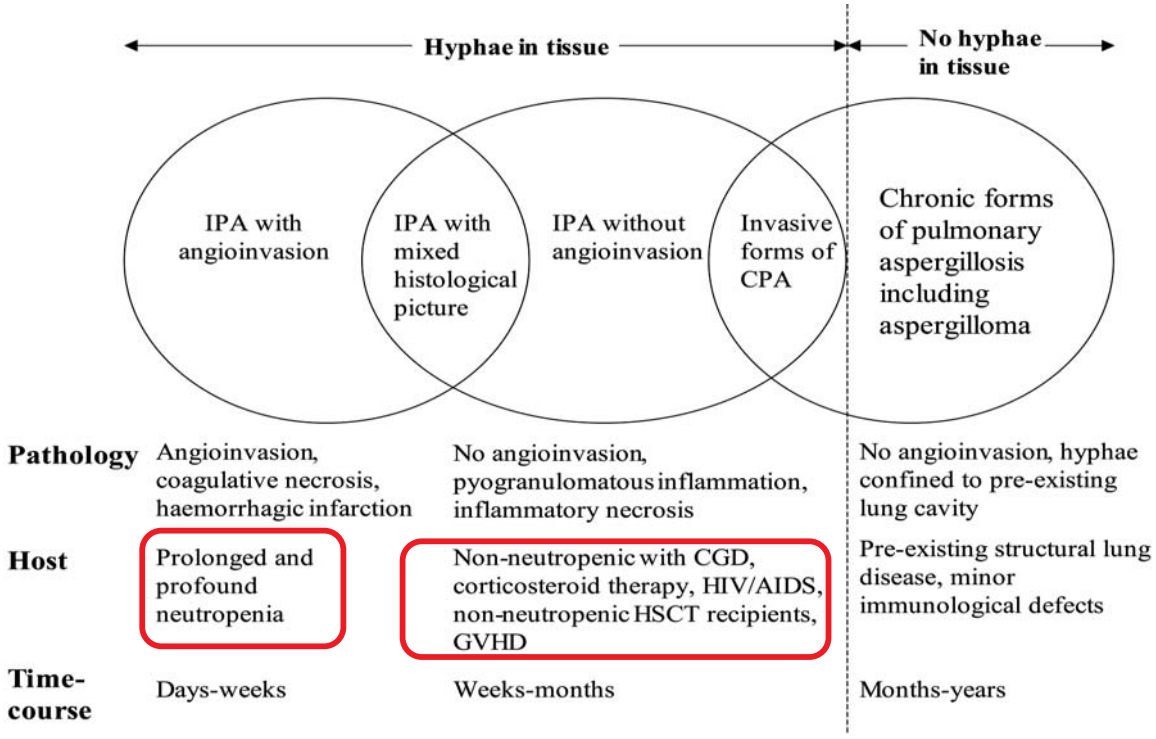
Hsu et al. Int J Infect Dis 2020
Tadolini et al. Eur Respir J 2020

Interaction of *Aspergillus* with host



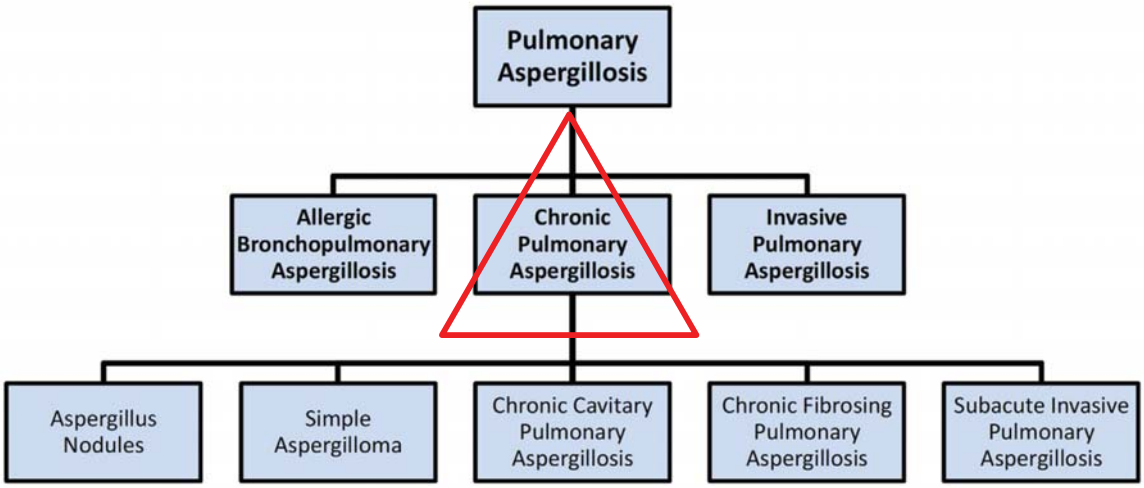
Kosmidis et al. Thorax 2015

IPA VS CPA



Kosmidis C, et al. Thorax. 2015

Clinical Spectrum of Pulmonary Aspergillosis



Kanj et al. Respir Med 2018

Chronic pulmonary aspergillosis is found in non-immunocompromised patients with prior or current lung disease

Denning et al. Eur Respir J 2016

Underlying conditions in CPA

Surgical treatment for pulmonary aspergilloma: a 28 year experience

Jeng-Chang Chen, Yih-Leong Chang, Shi-Ping Luh, Jang-Ming Lee, Yung-Chie Lee

TABLE 3 Under … to literature

Underlying condition … nces of being an … for CPA

Classical tuberculosi… … 50%) of

Non-tuberculous myc… infection … [5] … ses [7] … ses [8]* … ses [9]+

ABPA±asthma … ses [7]

COPD and/or emphys… … [4]

Pneumothorax±bulla… … [5] … [4]

3/24 (12%) of CPA cases [5]

***Results* – The most common clinical presentation of pulmonary aspergilloma was haemoptysis which occurred in 61 patients (91.0%). Tuberculosis was the most common pre-existing disease, occurring in 54 patients (80.6%). The plain chest radio-**

Smith et al. Eur Respir J 2011

TABLE 3 Diagnostic criteria for different management of chronic pulmonary aspergillosis (CPA)

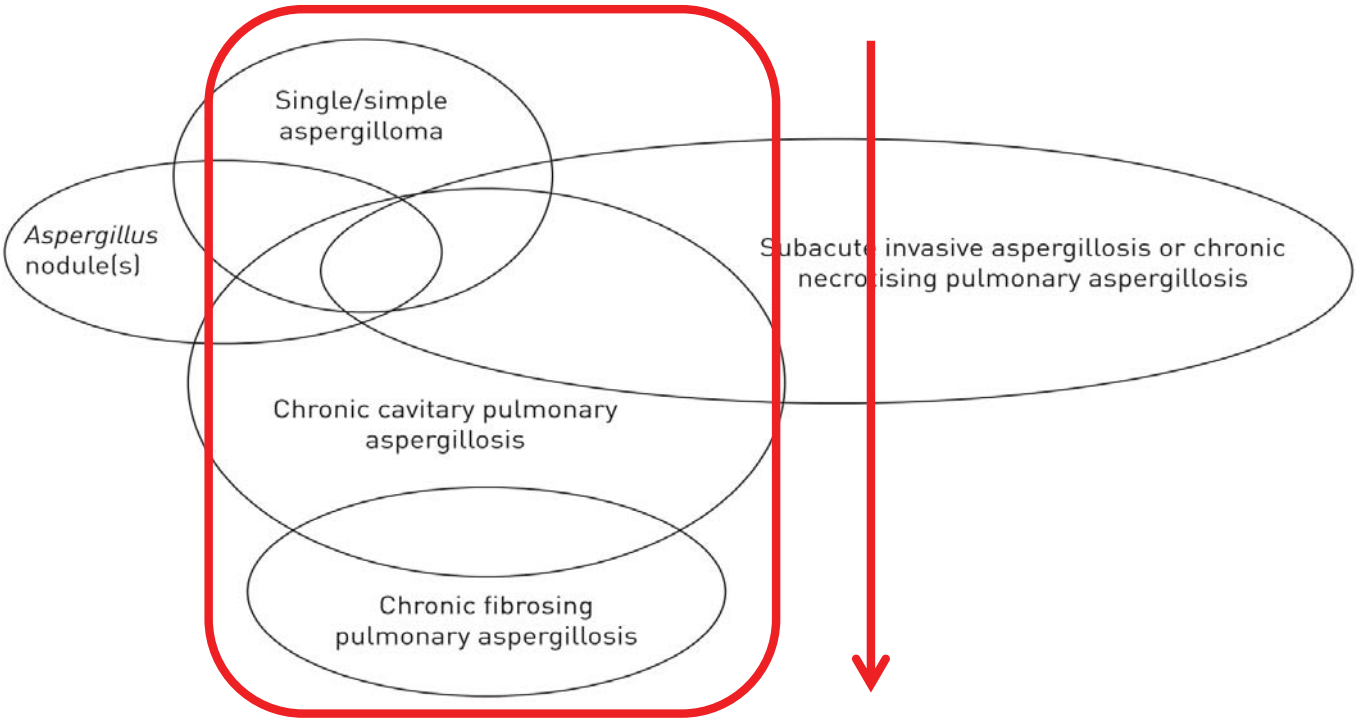
Term	Definition
Simple aspergilloma	Single pulmonary cavity containing a fungal ball, with serological or microbiological evidence implicating *Aspergillus* spp. in a non-immunocompromised patient with minor or no symptoms and no radiological progression over at least 3 months of observation.
CCPA	One or more pulmonary cavities (with either a thin or thick wall) possibly containing one or more aspergillomas or irregular intraluminal material, with serological or microbiological evidence implicating *Aspergillus* spp. with significant pulmonary and/or systemic symptoms and overt radiological progression (new cavities, increasing pericavitary infiltrates or increasing fibrosis) over at least 3 months of observation.
CFPA	Severe fibrotic destruction of at least two lobes of lung complicating CCPA leading to a major loss of lung function. Severe fibrotic destruction of one lobe with a cavity is simply referred to as CCPA affecting that lobe. Usually the fibrosis is manifest as consolidation, but large cavities with surrounding fibrosis may be seen.
***Aspergillus* nodule**	One or more nodules which may or may not cavitate are an unusual form of CPA. They may mimic tuberculoma, carcinoma of the lung, coccidioidomycosis and other diagnoses and can only be definitively diagnosed on histology. Tissue invasion is not demonstrated, although necrosis is frequent.
SAIA	Invasive aspergillosis, usually in mildly immunocompromised patients, occurring over 1–3 months, with variable radiological features including cavitation, nodules, progressive consolidation with "abscess formation". Biopsy shows hyphae in invading lung tissue and microbiological investigations reflect those in invasive aspergillosis, notably positive *Aspergillus* galactomannan antigen in blood (or respiratory fluids).

Most common

Most severe

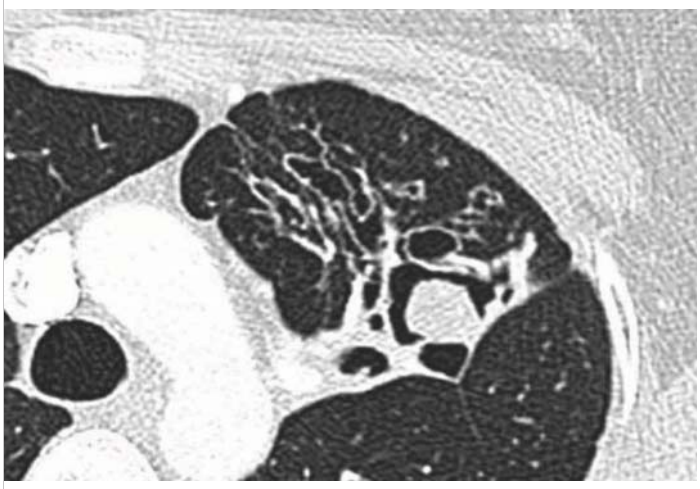
CCPA: chronic cavitary pulmonary aspergillosis; CFPA: chronic fibrosing pulmonary aspergillosis; SAIA: subacute invasive aspergillosis/chronic necrotising/semi-invasive.

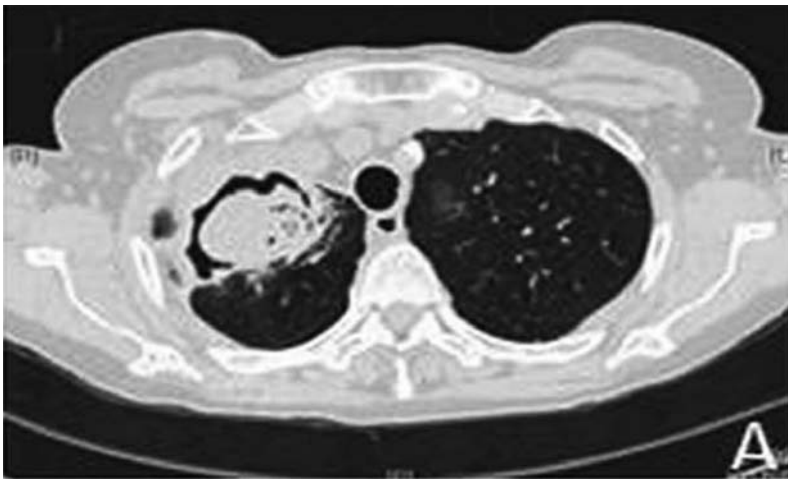
Types of chronic pulmonary aspergillosis



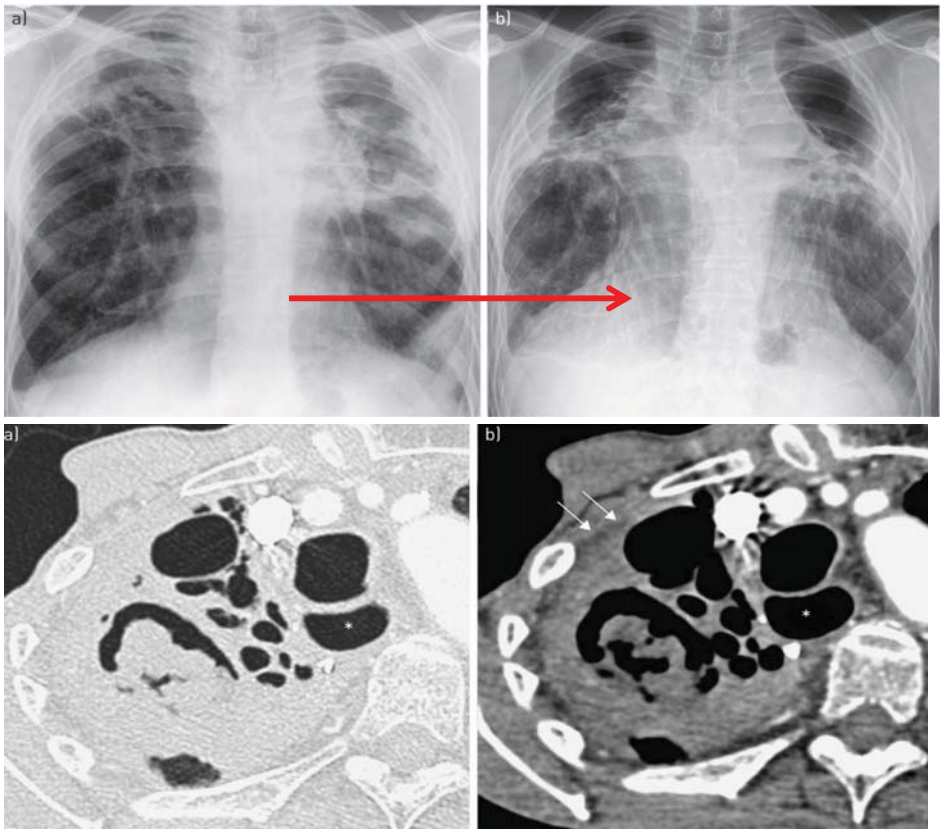
Denning et al. Eur Respir J 2016

Aspergilloma





Chronic cavitary pulmonary aspergillosis



Serial CXR change of CCPA

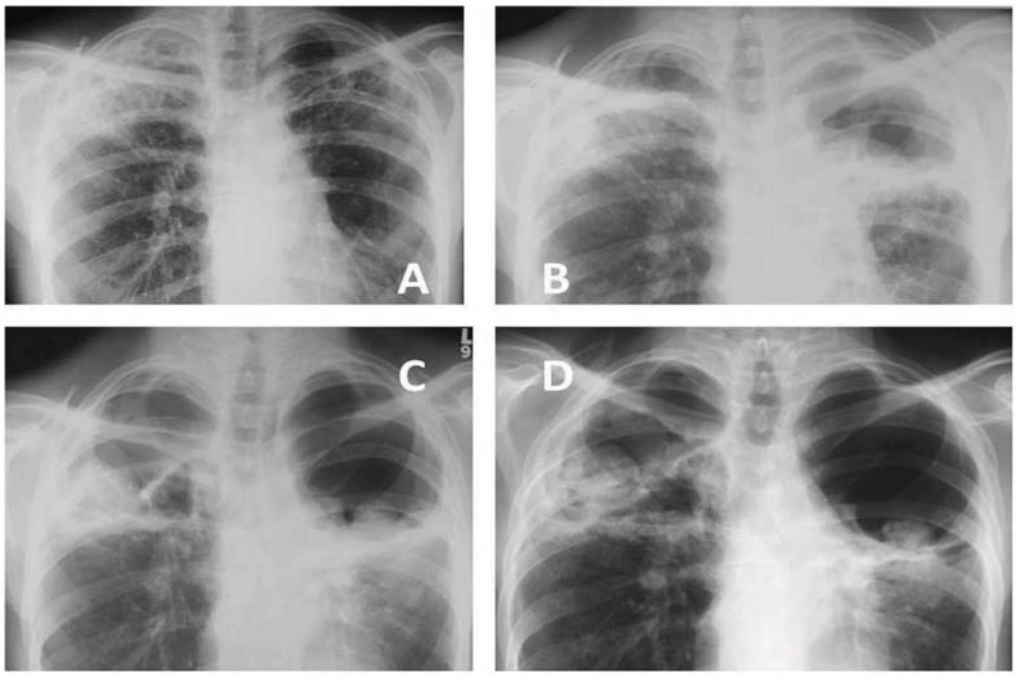
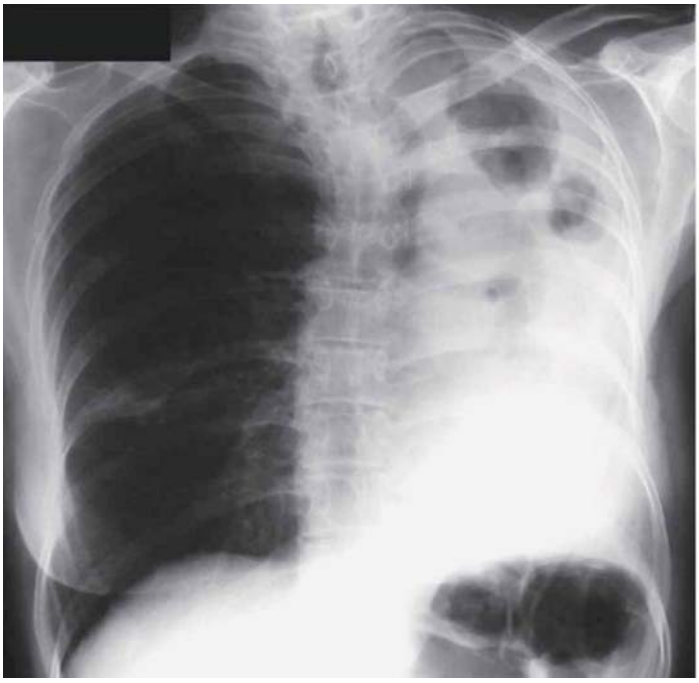
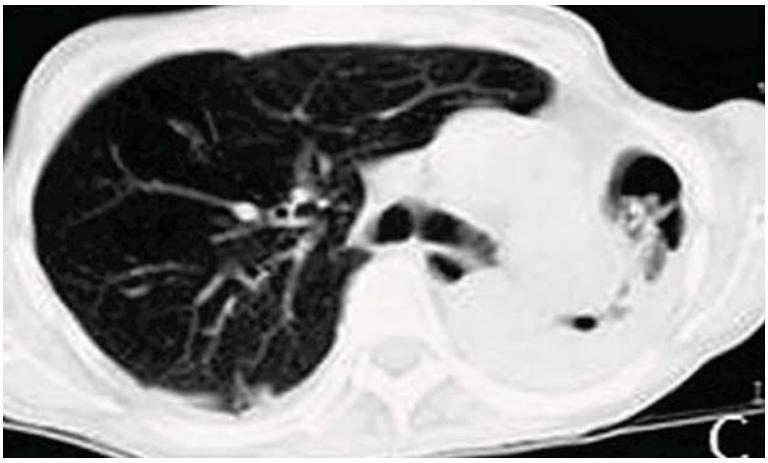


Figure 4 Serial chest X-rays of a patient with chronic cavitating pulmonary aspergillosis. (A) January 2001; (B) February 2002; (C) April 2003; (D) July 2003.

Chronic fibrosing pulmonary aspergillosis





The diagnosis of CPA requires a combination of characteristics:

1.Clinical symptoms

2.one or more cavities with or without a fungal ball present or nodules on thoracic imaging,

3. direct evidence of Aspergillus infection (microscopy or culture from biopsy) or an immunological response to Aspergillus spp.

exclusion of alternative diagnoses and all present for at least 3 months.

Clinical + Radiologic + Mycologic

Griffith et al. Am J Respir Crit Care Med 2007
Daley et al. Clin Infect Dis 2020

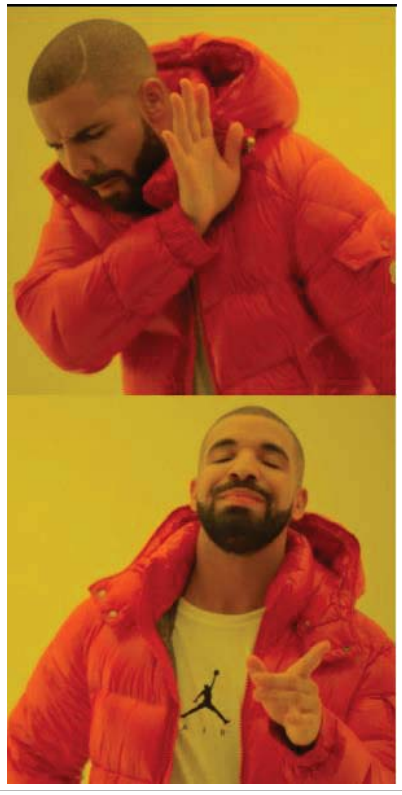
Pulmonary Aspergillosis in Taiwan-Claims Database

Fungal disease	ICD-9 Code	Taiwan, This Study **	
		Incident Case Number	Incidence Rate
Aspergillosis	117.3, 484.6	567	2.43
Pulmonary aspergillosis (PA)	484.6	228	0.98
PA post Tuberculosis (incidence)	484.6, 010-0.18	60	0.26
PA post Tuberculosis (prevalence)	484.6, 010-0.18	75*	0.32 *
Chronic pulmonary aspergillosis	None#	-	-
Allergic bronchopulmonary aspergillosis (ABPA)	518.6	45 *	0.19*
Severe asthma with fungal sensitization		-	-
Mucormycosis	117.7	66	0.28

Of pulmonary aspergillosis, 32.9% developed in patients with COPD and 26.3% had prior diagnosis of TB

Huang et al. J Fungi 2019

Clinical Dilemma In Diagnosis



切片，支氣管鏡

抽血

Mycological evidence

TABLE 4 Key tests on respiratory samples for patients with cavitary or nodular pulmonary infiltrate in non-immunocompromised patients

Test	Strength of recommendation	Quality of evidence
Direct microscopy for hyphae [#]	A	II
Fungal culture (sputum or BAL) [¶]	A	III
Histology	A	II
Fungal culture (transthoracic aspiration)	B	II
***Aspergillus* PCR (respiratory secretion)** [+]	C	II
Bacterial culture (sputum or BAL)	C	IIt

BAL: bronchoalveloar lavage. [#]: positive microscopy is a strong indicator of infection; [¶]: bacterial culture plates are less sensitive than fungal culture plates; [+]: PCR more sensitive than culture.

The presence of *A. fumigatus* in a bronchoscopic specimen is far more common in infection compared to colonisation

Denning et al. Eur Respir J 2016

Galactomannan (GM) antigen test

Serum or Bronchoalveolar lavage (BAL)

	Specimen	Sensitivity (%)	Specificity (%)	Note
Galactomannan	Serum	22.6–66.7	63.5	Cut off values differ in each study between 0.5 and 1.0
	BAL	77.2–77.8	77–90	Cut off values differ in each study between 0.4 and 0.5

BAL GM possibly better than serum

Takozono et al. Front Microbiol 2018

Mycological evidence

GM test (Serum)

168/334

Table 2 Diagnostic performance of the serum galactomannan (GM) antigen test at various cut-off indexes.

Cut-off index	0.25	0.5	0.75	1.0
Sensitivity (%)	63.1 (55.3–70.4)	22.6 (16.5–29.7)	11.9 (7.4–17.8)	8.9 (5.1–14.3)
Specificity (%)	34.9 (27.7–42.7)	84.9 (78.6–90)	92.8 (87.7–96.2)	95.8 (91.5–98.3)
Likelihood ratio (+)	0.97 (0.826–1.14)	1.5 (0.951–2.37)	1.65 (0.832–3.26)	2.12 (0.886–5.06)
Likelihood ratio (−)	1.(		1.02)	0.951 (0.898–1.01)
Area under the ROC curve	0.4		0.555)	0.524 (0.497–0.55)

The data are presented as values ar
ROC, receiver operating characteris

BAL, please!

TABLE 5 Contribution of antigen to the diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis of exclusion of CPA	Antigen BAL	B	II	Antigen studied in BAL and serum, but not in sputum
		Antigen (serum)	C	II	
		Antigen (sputum)	No data		

Shin et al. J Infect 2014[29]

Optimal Cut-off Value of BAL GM Test

TABLE 4 Studies evaluating the role of serum and BALF-GM index for diagnosing CPA[a]

Source/yr	Study design	No. of controls	No. of subjects with CPA	BALF-GM index cutoff	Sensitivity (%) of BALF-GM	Specificity (%) of BALF-GM
Nguyen et al. (13)/2007	Retrospective	67	2 (SAIA), 2 (SA)	≥1	100*	88.1
				≥2.5	50*	95.5
Kitasato et al. (15)/2009	Retrospective		16 (SAIA), 12 (SA)			
Park et al. (14)/2011	Retrospective		48 (SA)	≥0.5	92	
Izumikawa et al. (21)/2012	Retrospective	126	18	≥0.4	72.2	77
Shin et al. (20)/2014	Retrospective	166	168			
Urabe et al. (22)/2017	Retrospective	120	28	≥0.5	77.8	90
Current study	Prospective	72 (45 for serum GM, 27 for BALF-GM)	243	>2.5	50	100

Proposed BAL GM cut-off value ranged from 0.4 to 2.5

Segal et al. J Clin Microbiol 2019

Mycological evidence

GM test (Serum VS BAL)

Table 3 Sensitivity, specificity, positive predictive value, and negative predictive value of galactomannan antigen test.

	Serum (%)	BALF (%)
Sensitivity	66.7	72.2
Specificity	63.5	77.0
PPV	20.7	31.0
NPV	93.0	95.1

Cut off point
Serum:0.7
BAL: 0.4

PPV, positive predictive value; NPV, negative predictive value.

Izumikawa et al. Med Mycol.2012

Mycological evidence

Aspergillus Ab

Antibody diagnosis of CPA

Detection of *Aspergillus* antibodies is a key diagnostic feature of CPA (table 6). The presence of anti-*Aspergillus* antibodies differentiates between infected and colonised patients with a positive predictive value of 100% for detecting infection [29]. Numerous commercial assays are available, in addition to some

TABLE 6 Antibody diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis or exclusion of CPA	*Aspergillus* IgG antibody	A	II	IgG and precipitins test standardisation incomplete
		Aspergillus precipitins	A	II	Mostly in-house tests and poorly validated; uncertain sensitivity is the major problem
		Aspergillus IgM antibody	D	III	Few data
		Aspergillus IgA antibody	D	III	

Denning DW, et al. ERJ 2016

Performance of Aspergillus IgG Assay

Table 3 Results in CPA cases and healthy controls.

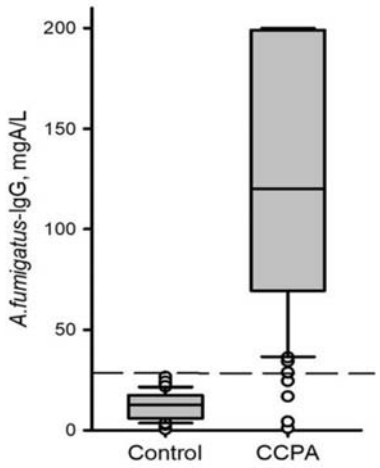
Test (Unit)	Controls range (n = 100)	CPA range (n = 241)	Controls mean	CPA mean	Controls median	CPA median	Frequency of positive results by manufacturer's guidelines in controls (intermediate results)	Frequency of positive results by manufacturer's guidelines in CPA (intermediate results)	ROC AUC	95% CI
Dynamiker (AU/ml)	16–88	23–6118	37	341	34	124	6% (11%)	78% (5%)	0.918	0.89–0.946
Genesis (U/ml)	0–20	1–930	7	111	6	60	22% (13%)	82% (5%)	0.902	0.871–0.933
Immulite (mg/L)	0–35	3–7660	5	678	4	392	n/a[a]	n/a[a]	0.991	0.982–1
ImmunoCAP mg/L	0–36	9–1707	6	216	5	126	0%[b]	88%[b]	0.996	0.992–1
Serion (U/ml)	0–40	4–3436	10	232	6	131	0% (0%)	74% (10%)	0.973	0.96–0.987
Precipitins	All negative	Negative to 1:32	–	–	–	–	0%	59%	–	–

[a] There is no recommended cut off for Immulite at the time of publication.
[b] Results for ImmunoCAP reported against the cutoff of 40 mg/L recommended for use in UK labs at the time of publication.

Page et al. J Infect 2016

TABLE 3 Sensitivity and specificity of *Aspergillus fumigatus*-specific IgG (by Phadia ImmunoCap) in the current cohort (all patients) for diagnosing chronic pulmonary aspergillosis (CPA) using cut-off values derived from previous studies

Author/year	Basis of cut-off chosen	No. of controls	Cut-off value	Sensitivity (95% CI), (%)	Specificity (95% CI), (%)	Youden's J
Van Hoeyveld et al[10] 2006	Healthy controls	42	35 mgA/L	89.8 (83.5-94.3)	100 (92.9-100)	0.898
	Diseased controls	199	70 mgA/L	72.3 (63.9-79.6)	100 (92.9-100)	0.723
Baxter et al[9] 2012	Manufacturer's instruction	-	40 mgA/L	84.7 (77.5-90.3)	100 (92.9-100)	0.847
Page ID et al[8] 2016	Healthy blood donors (High TB burden)	100	20 mgA/L	95.6 (90.7-98.4)	90 (78.2-96.7)	0.856
Page ID et al[7] 2018	Healthy controls (low TB burden)	114	50 mgA/L	79.6 (71.8-85.9)	100 (92.9-100)	0.796
Current study	Diseased controls (High TB burden)	50	27 mgA/L	94.2 (88.8-97.5)	100 (92.9-100)	0.942



Promising diagnostic tool??

Sehgal et al. Mycoses 2018

Aspergillus IgM

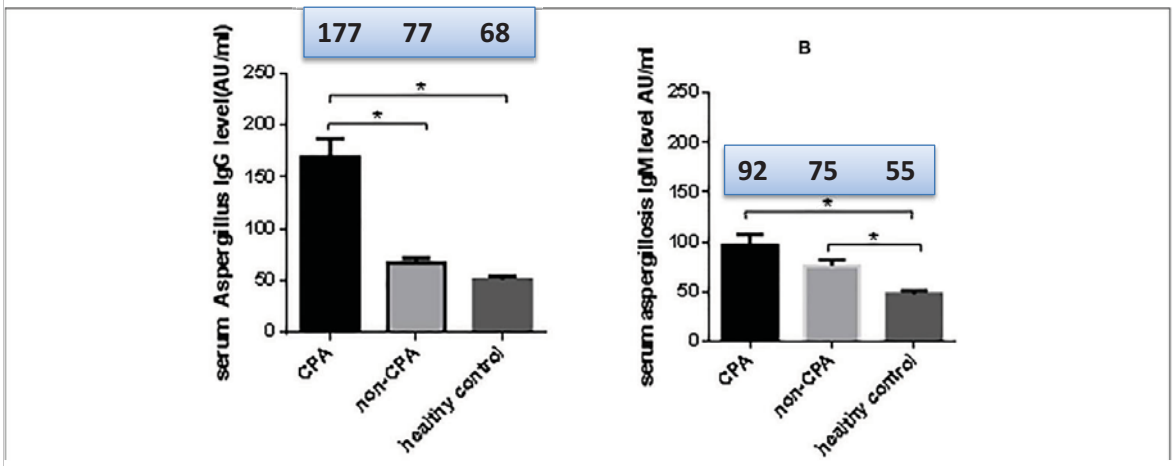


TABLE 2 | Diagnostic performance of As-IgG and As-IgM and BALF GM.

	As-IgG	As-IgM	BALF GM (ODI ≥ 0.7)	Combination of As-IgG and As-IgM
sensitivity	84.1%	43.9%	79.1%	95.1%
specificity	89.6%	87.2%	84.2%	76.8%
PPV	84.1%	69.2%	87.5%	72.9%
NPV	89.6%	70.3%	86.3%	96.0%
false positive rate	15.9%	30.7%	15.8%	23.2%
false negative rate	10.4%	29.7%	20.9%	4.0%

IgG performs better than IgM

Li et al. Front Microbiol 2019

Taiwan Local Epidemiologic Data

Not readily available

	Healthy control (n=200)	TB-related group				p value*
		All (n=1042)	TB contacts (n=326)	Active TB (n=524)	Old TB (n=192)	
Age	54.7±11.8	51.8±20.0	38.2±16.9	56.1±18.4	63.2±16.4	<0.001
<45	42 (21.0)	387 (37.1)	201 (61.7)	155 (29.6)	31 (16.2)	<0.001
45-65	123 (61.5)	351 (33.7)	107 (32.8)	184 (35.1)	60 (31.3)	
>65	35 (17.5)	304 (29.2)	18 (5.5)	185 (35.3)	101 (52.6)	
Body mass index	NA	22.2±3.55	23.2±3.7	21.7±3.27	21.5±3.7	<0.001
<18	NA	103 (9.9)	17 (5.2)	57 (10.9)	29 (15.1)	<0.001
18-25	NA	740 (71.0)	229 (70.3)	389 (74.2)	122 (63.5)	
>25	NA	199 (19.1)	80 (24.5)	78 (14.9)	41 (21.4)	
Male: female (n)	100:100	611:431	161:165	329:195	121:71	<0.001

	TB-related group				
	All (n=1042)	TB contacts (n=326)	Active TB (n=524)	Old TB (n=192)	p value*
Underlying diseases					
Diabetes mellitus	149 (14.3)	7 (2.2)	93 (17.8)	49 (25.5)	<0.001
ESRD	21 (2.0)	1 (0.3)	10 (1.9)	10 (5.2)	<0.001
Malignancy	95 (9.1)	4 (1.2)	69 (13.2)	22 (11.5)	<0.001
Autoimmune disease	24 (2.3)	0	21 (4.0)	3 (1.6)	<0.001
Hypertension	210 (20.2)	14 (4.3)	117 (22.3)	79 (41.2)	<0.001
Rural residence	90 (8.6)	20 (6.1)	48 (9.2)	22 (11.5)	0.095
Smoking	368 (35.3)	63 (19.3)	220 (42.0)	85 (44.3)	<0.001
Current smoker	186 (17.9)	39 (12.0)	101 (19.3)	46 (24.0)	<0.001
Ever smoker	182 (17.5)	24 (7.4)	119 (22.7)	39 (20.3)	
Never smoker	674 (64.7)	263 (80.7)	304 (58.0)	107 (55.7)	

	Healthy control (n=200)	TB-related group				
		All (n=1042)	TB contacts (n=326)	Active TB (n=524)	Old TB (n=192)	p value*
Chest CT available	NA	507 (48.7)	6 (1.8)	360 (68.7)	141 (73.4)	<0.001
Chest image findings						
Cavitation	NA	86 (8.3)	0	54 (10.3)	32 (16.7)	<0.001
Fibro-nodule	NA	483 (46.4)	15 (4.6)	337 (64.3)	131 (68.2)	<0.001
Consolidation	NA	165 (15.8)	4 (1.2)	132 (25.2)	29 (15.1)	<0.001
Infiltrates	NA	375 (36.0)	23 (7.1)	280 (53.4)	72 (37.5)	<0.001

	Healthy control (n=200)	TB-related group				
		All (n=1042)	TB contacts (n=326)	Active TB (n=524)	Old TB (n=192)	p value*
A. fumigatus IgG						
Titer (mgA/L)	28.6±27.4	26.6±27.9	28.4±27.6	22.6±20.2	34.4±41.5	<0.001
Titer >50 mgA/L	30 (15.0±2.5)	136 (13.1±1.0)	56 (17.2±2.1)	48 (9.2±1.3)	32 (16.7±2.7)	<0.001
Titer >40 mgA/L	44 (22.0±2.9)	195 (18.7±1.2)	75 (23.0±2.3)	76 (14.5±1.5)	44 (22.9±3.0)	0.002
Titer >27 mgA/L	66 (33.0±3.3)	345 (33.1±1.5)	123 (37.7±2.7)	139 (26.5±1.9)	83 (43.2±3.6)	<0.001
Titer >20 mgA/L	95 (47.5±3.5)	476 (45.7±1.5)	153 (46.9±2.8)	216 (41.2±2.2)	107 (55.7±3.6)	0.002
A. niger IgG titer (mgA/L)	20.3±21.3	19.5±18.9	21.3±22.0	17.9±16.3	20.7±19.4	0.023

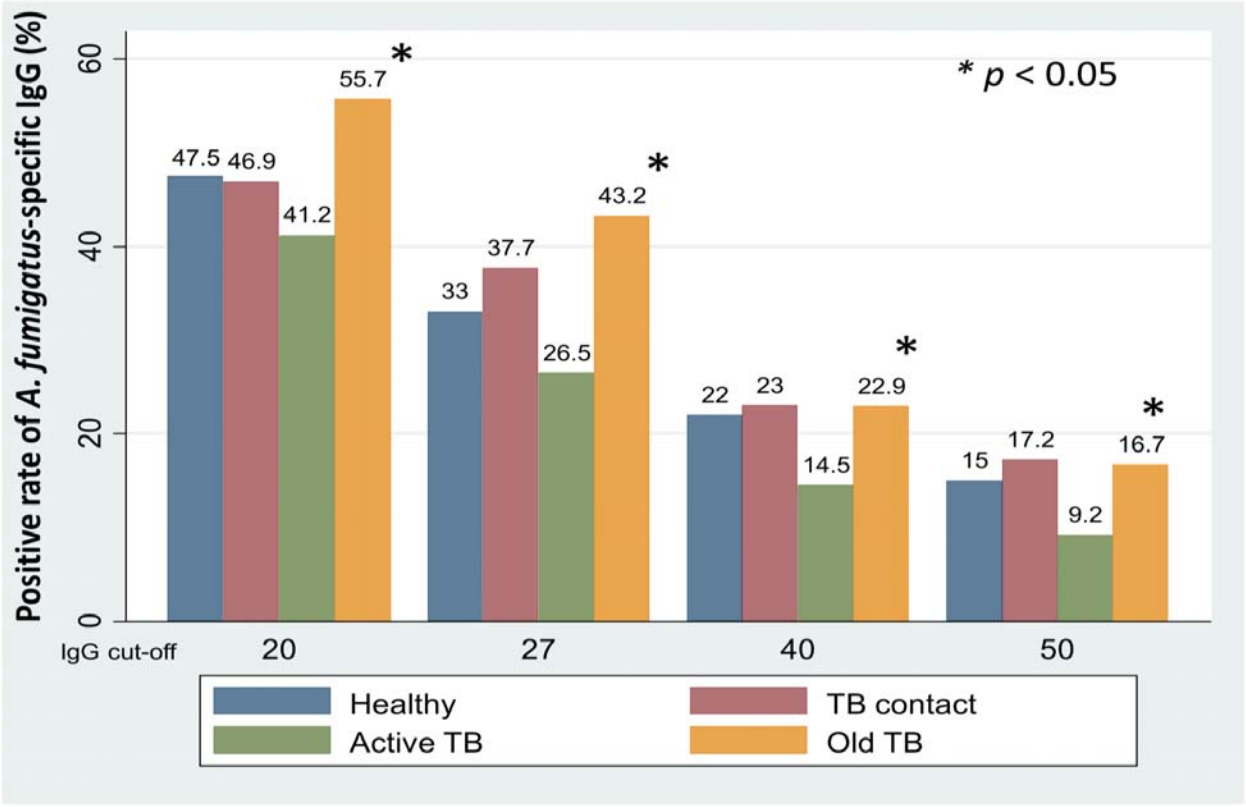
Independent factors associated with *A. fumigatus*-specific IgG positivity in logistic regression

Variables	Crude OR	95% CI	p value	Adjusted OR	95% CI	p value
Age						
<45 (Ref) Higher						
45-65	0.59	0.43-0.80	<0.001	0.56	0.41-0.78	<0.001
>65	0.64	0.47-0.88	0.006	0.63	0.44-092	0.014
TB status						
Close contacts (Ref)						
Active TB	0.60	0.44-0.80	<0.001	0.69	0.50-0.95	0.025
Old TB Higher	1.26	0.87-1.81	0.22	1.59	1.05-2.42	0.030
End-stage renal disease	0.21	0.05-0.90	0.035	0.19	0.04-0.85	0.029
Lower						
Pulmonary cavitation	1.51	0.96-2.36	0.073	1.73	1.07-2.80	0.025
Higher						
Female sex	1.49	1.14-1.93	0.003	1.49	1.14-1.95	0.004
Higher						

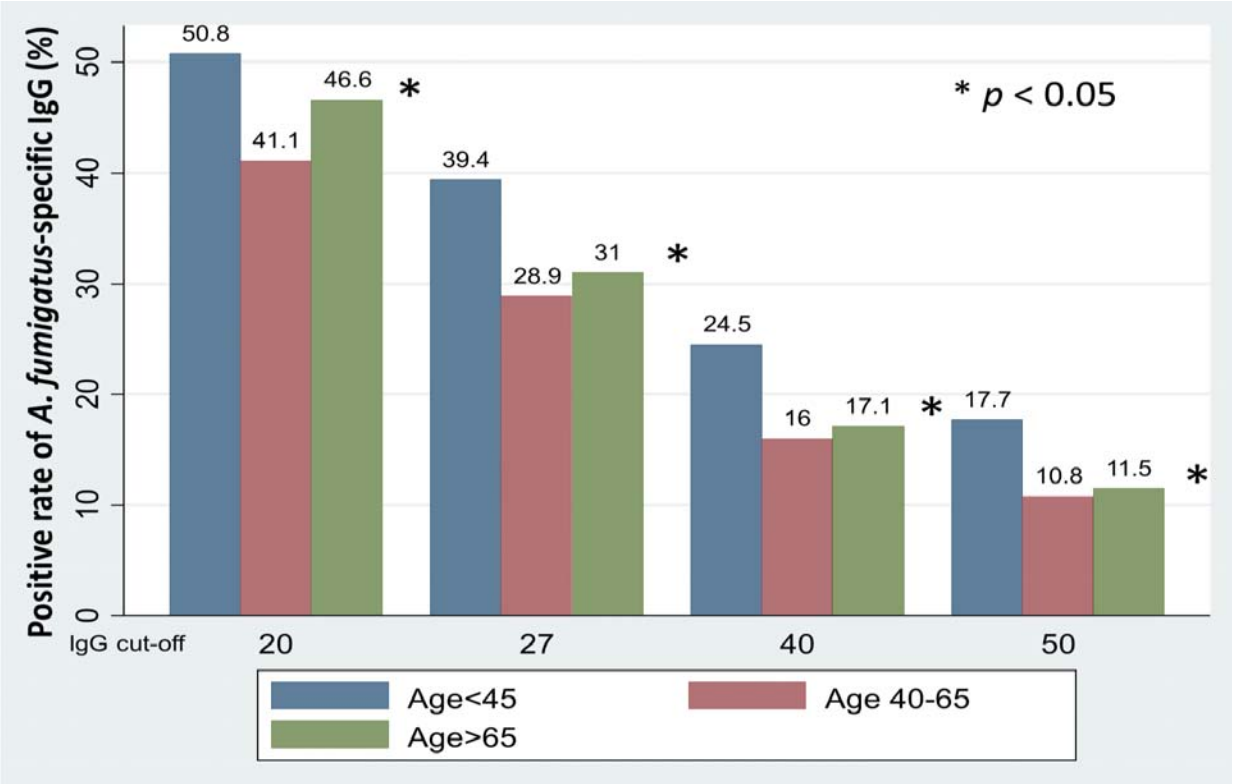
Independent factors associated with A. fumigatus-specific IgG positivity in logistic regression (cut-off level at 50 mgA/L)

Variables	Crude OR	95% CI	*p* value	Adjusted OR*	95% CI	*p* value
Age						
<45 (Ref)						
45-65	0.46	0.29-0.71	<0.001	0.49	0.31-0.77	0.002
>65	0.59	0.38-0.92	0.019	0.65	0.39-1.08	0.098
TB status						
Close contacts (Ref)						
Active TB	0.50	0.33-0.75	<0.001	0.63	0.40-0.98	0.041
Old TB	1.03	0.64-1.65	0.920	1.38	0.80-2.37	0.247
Female sex	1.69	1.17-2.43	0.005	1.63	1.12-2.35	0.010
Cancer	0.29	0.10-0.79	0.016	0.39	0.14-1.09	0.073
Lower						
Rural residency	1.59	0.91-2.79	0.106	1.69	0.95-3.02	0.075
Higher						

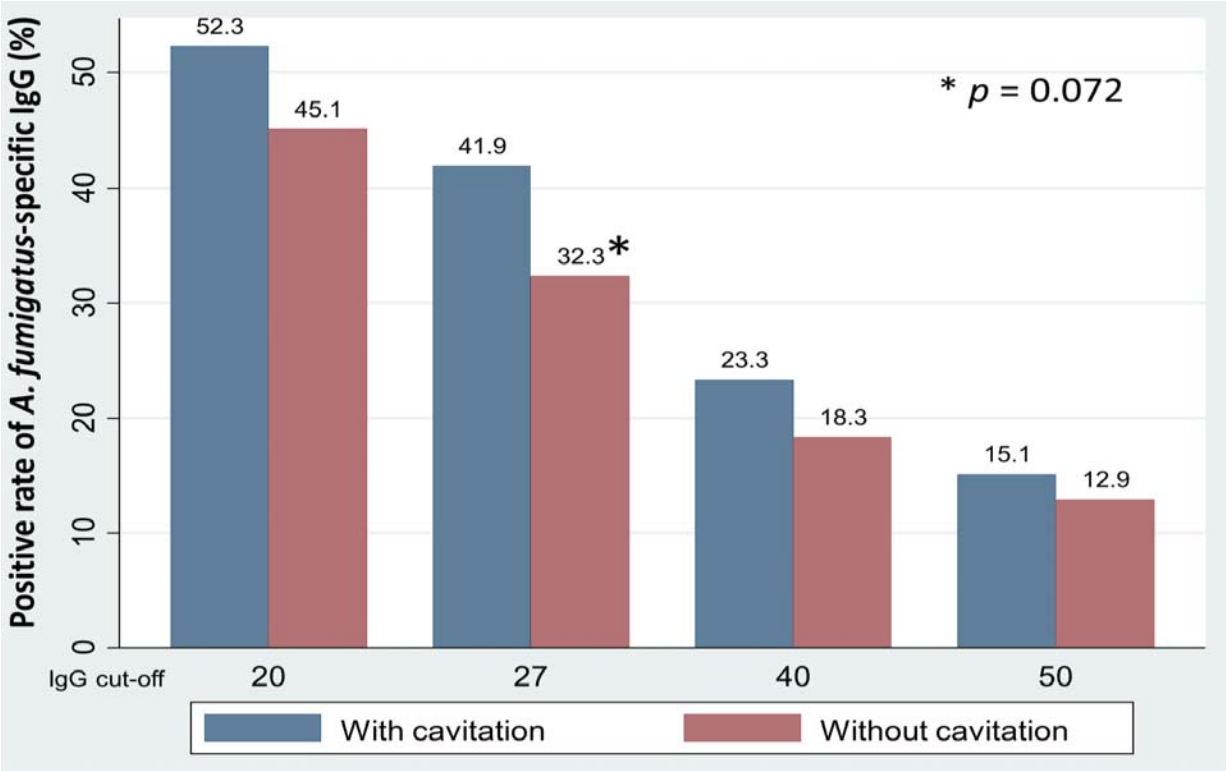
Proportion of *Aspergillus fumigatus* IgG positivity under different cut-off values among different TB status



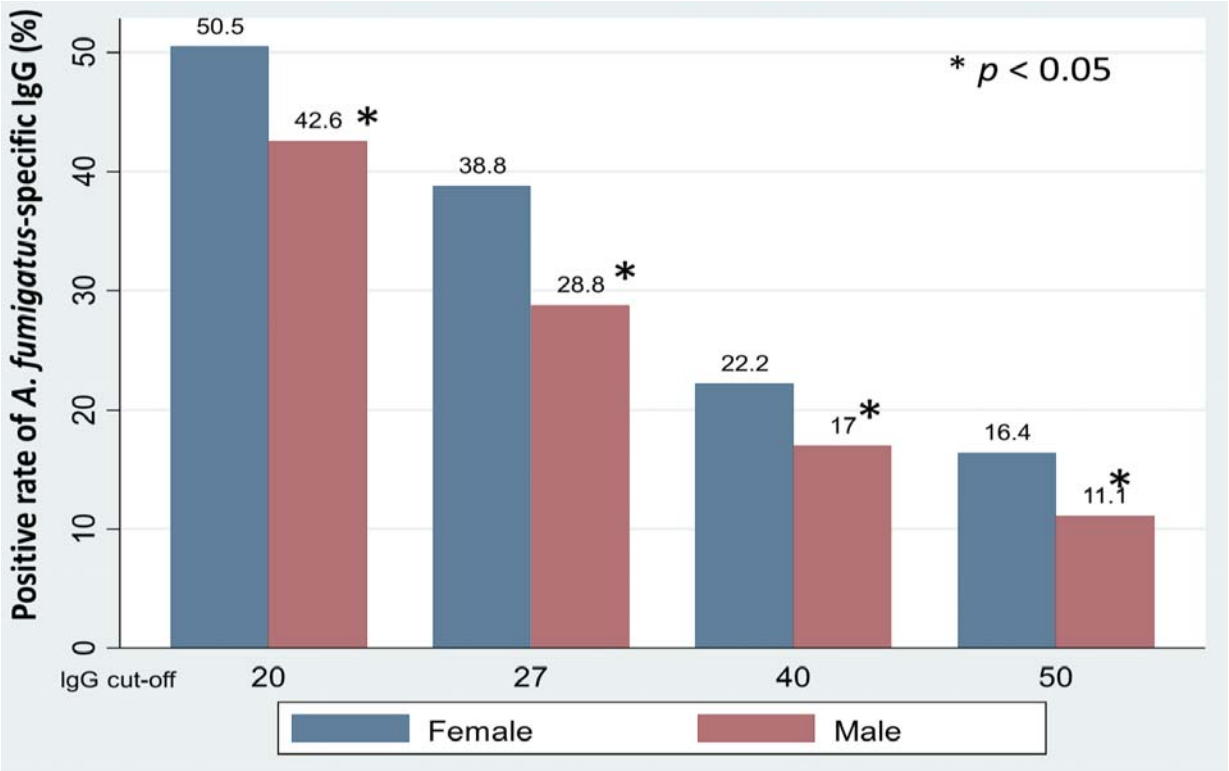
Proportion of *Aspergillus fumigatus* IgG positivity under different cut-off values among different age groups



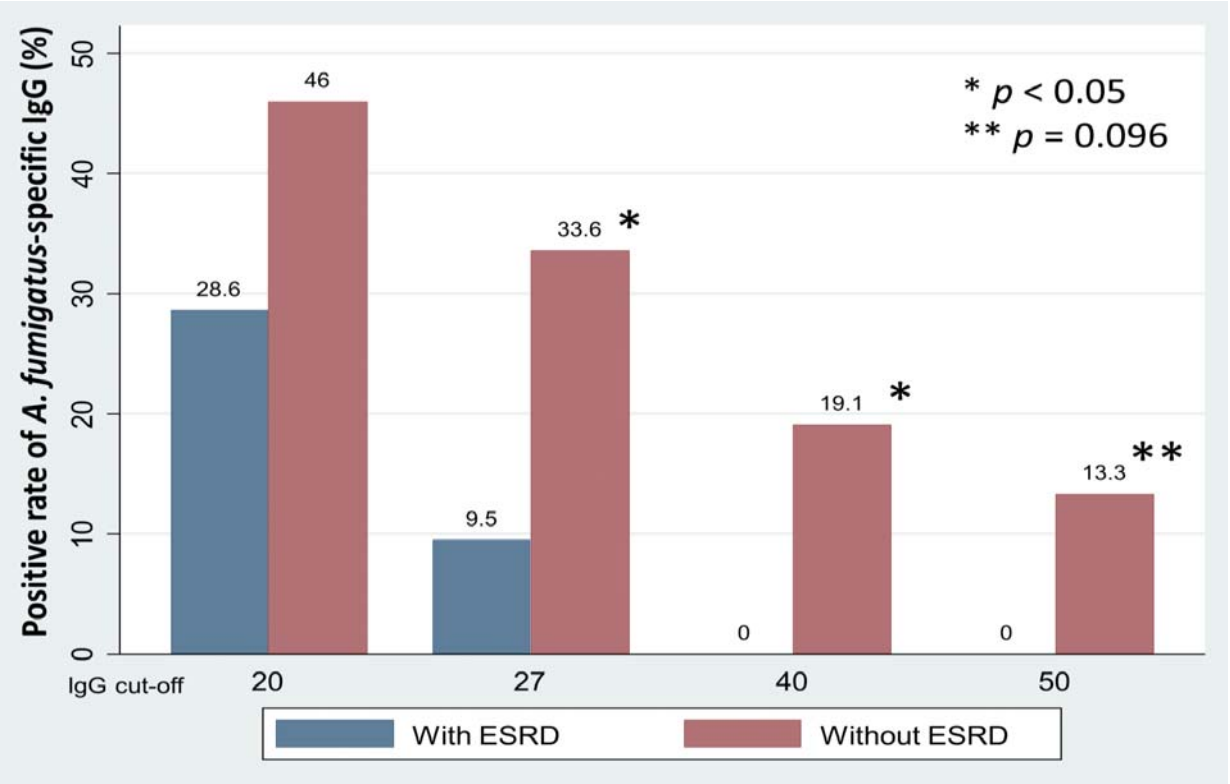
Proportion of Aspergillus fumigatus IgG positivity under different cut-off values among patients with/without cavitation



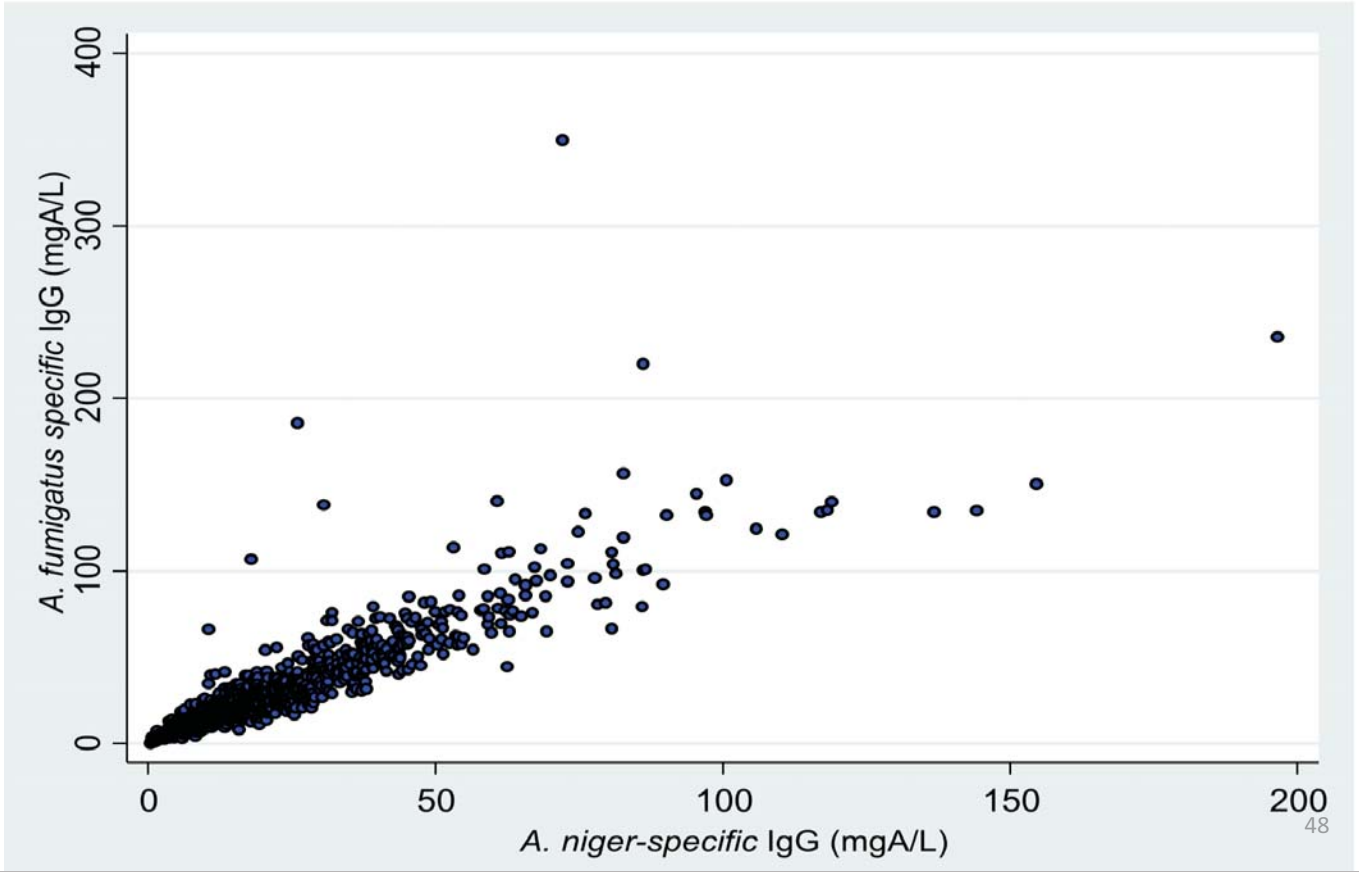
Proportion of *Aspergillus fumigatus* IgG positivity under different cut-off values among male/female



Proportion of *Aspergillus fumigatus* IgG positivity under different cut-off values among ESRD/non-ESRD



Spearman correlation coefficient: 0.942



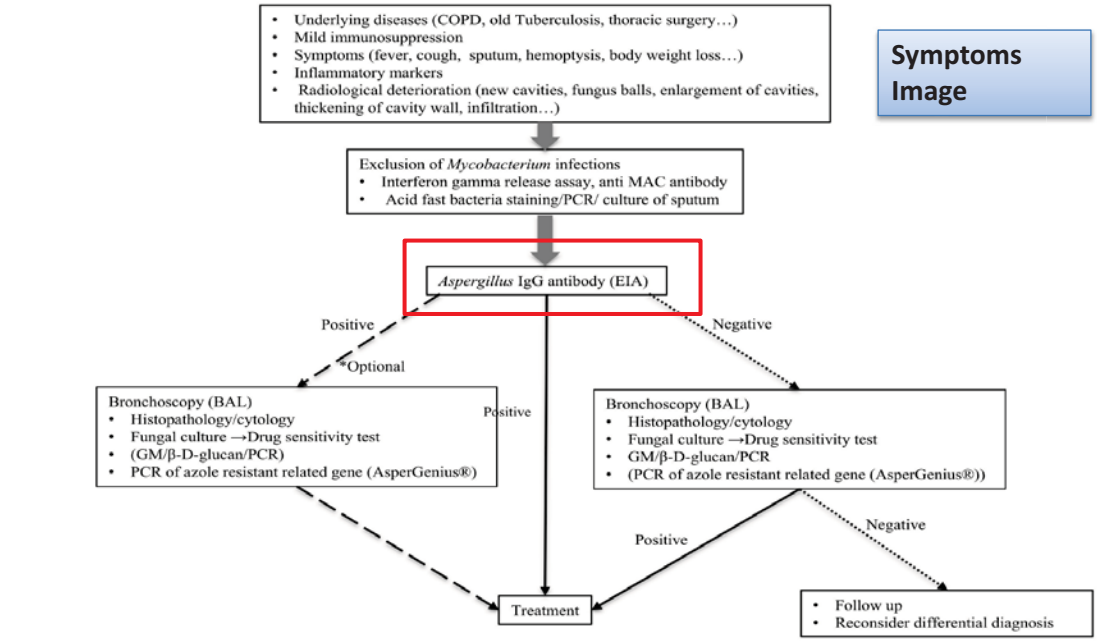
	TB status	Age /sex	Comorbidity	Timing of sampling IgG related to CPA diagnosis	Interval between CPA and end of TB treatment	A. fum / A. nig IgG (mgA/L)	Symptom	Mycologic evidence	Type of CPA	Imaging findings
Case 1	Active TB	65/M	Rheumatoid arthritis	15 months before CPA diagnosis	6 months	48.9/37.6	Cough, sputum	BAL: *A. niger*	CCPA	Left upper lung cavitation with wall thickening
Case 2	Old TB	45/M	NPC, HTN	10 months under CPA treatment	3.5 years	46.1/32.8 *	Cough, sputum, fever	Positive BAL (5.74) and serum (1.53) GM antigen	CCPA	Diffuse Cavities, nodules with bronchiectasis, fibrosis and emphysema over bilateral lung
Case 3	Old TB	71/F	DM	Before CPA treatment	3 years	156.4/82.7	Cough, sputum, hemoptysis	Positive BAL GM antigen (1.21)	CCPA	Multiple cavities over RUL, right middle lobe collapse, fibrosis with bronchiectasis over bilateral lung
Case 4	Old TB	67/M	DM, HTN	Before CPA treatment	11 years	85.3/45.3	Cough, sputum, dyspnea	Positive serum GM antigen (1.06)	CFPA	Extensive fibrosis with diffuse bronchiectasis over bilateral lung
Case 5	Old TB	80/M	DM, HTN	Before CPA treatment	>20 years	134.0/97.0	Cough, sputum, dyspnea, hemoptysis	Positive BAL GM antigen (5.43) BAL: *A. terreus*	CCPA	Cavitation, bronchiectasis

The Incidence Rate of CPA in Taiwan TB Patients

- Median follow-up for 2.5 years and only one (0.2%) developed CPA during follow-up (71 events per 100,000 person-years)

- 285 TB patients two years after anti-TB treatment in Uganda for CPA surveillance and revealed 14 (4.9%) developed CPA with an incidence rate of 2,456 per 100,000 person-years.-> 26% had CXR visible cavitation

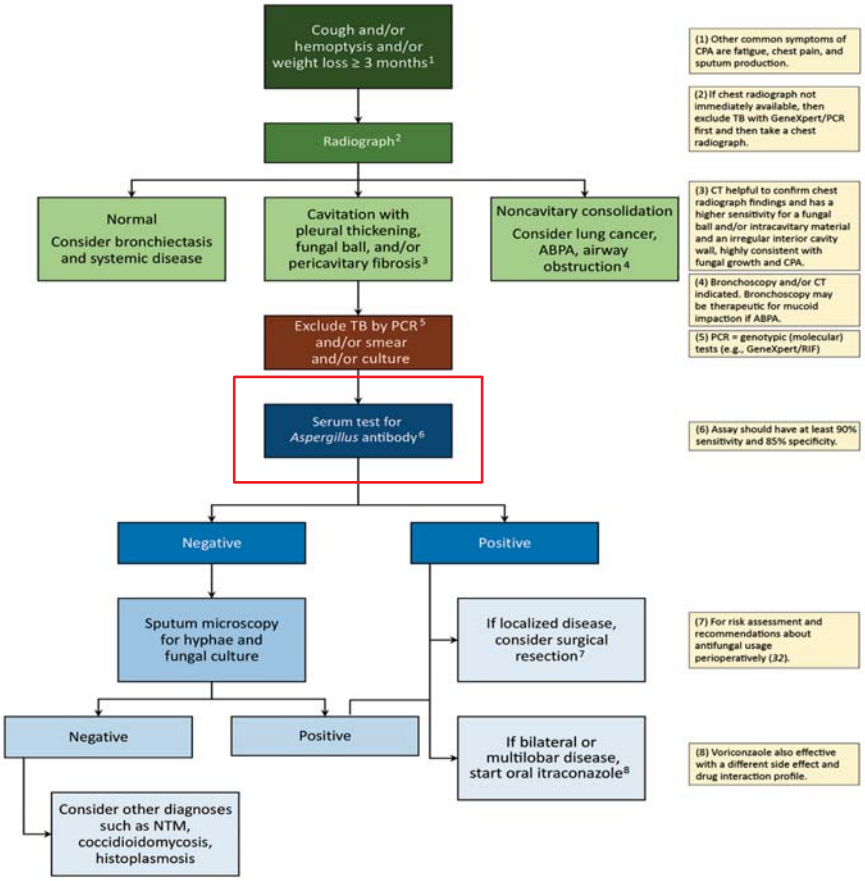
The Role of IgG in CPA Diagnosis



Symptoms Image

FIGURE 1 | Proposed algorithm for the diagnosis of chronic pulmonary aspergillosis. BAL, bronchoalveolar lavage.

Takozono T, et al. Front Microbiol 2018



Clinical suspicion is the first step

Denning et al. Emerg Infect Dis 2018

Nontuberculous Mycobacterium Lung Disease

Journal of the Formosan Medical Association (2020) 119, S1–S3

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

Highlights

Time to be familiar with nontuberculous mycobacterial lung disease - An emerging disease with diverse clinical outcomes

A serial of review articles in Taiwan, 2020

Nontuberculous mycobacterial lung disease epidemiology in Taiwan: A systematic review

Meng-Rui Lee [a,b], Lih-Yu Chang [a], Jen-Chung Ko [a,b], Hao-Chien Wang [b], Yi-Wen Huang [c,*]

Treatment for *Mycobacterium abscessus* complex—lung disease

Ya-Wei Weng [a], Chun-Kai Huang [b,c], Cheng-Len Sy [a], Kuan-Sheng Wu [a,d], Hung-Chin Tsai [a,d,e], Susan Shin-Jung Lee [a,d,*]

Treatment for *Mycobacterium avium* complex lung disease

Sheng-Wei Pan [a,b,c], Chin-Chung Shu [d,e], Jia-Yih Feng [a,b], Wei-Juin Su [a,b,*]

Treatment of pulmonary disease caused by *Mycobacterium kansasii*

Hung-Ling Huang [a,b,c,d], Po-Liang Lu [b,c,f], Chen-Hsiang Lee [g,h], Inn-Wen Chong [a,b,c,e,*]

Identification and drug susceptibility testing for nontuberculous mycobacteria

Wei-Chang Huang [a,b,c,d], Ming-Chih Yu [e,f,1], Yi-Wen Huang [g,h,*,1]

Nonpharmacological treatment for patients with nontuberculous mycobacterial lung disease

Chou-Chin Lan [a], Sheng-Ru Lai [b], Jung-Yien Chien [c,*]

Host immune response against environmental nontuberculous mycobacteria and the risk populations of nontuberculous mycobacterial lung disease

Chin-Chung Shu [a,b], Ming-Fang Wu [c,d], Sheng-Wei Pan [e,f], Ting-Shu Wu [g,*], Hsin-Chih Lai [h,i,**], Meng-Chih Lin [j]

Clinical relevance and diagnosis of nontuberculous mycobacterial pulmonary disease in populations at risk

Jia-Yih Feng [a,b], Wei-Chih Chen [a,b,c], Ying-Ying Chen [d], Wei-Juin Su [a,b,*]

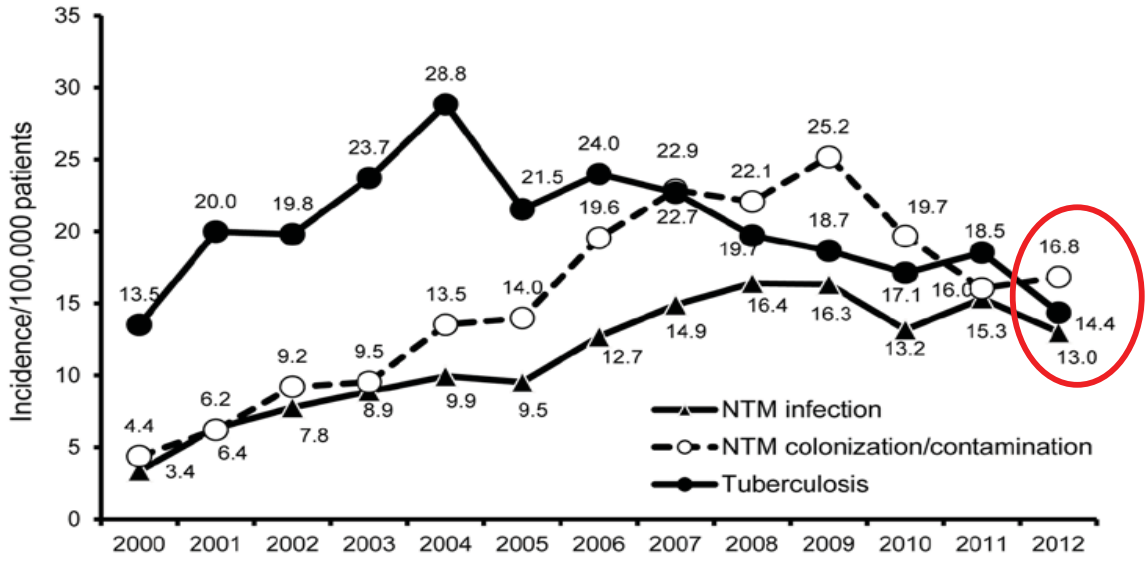
Recent advances and controversies in surgical intervention of nontuberculous mycobacterial lung disease: A literature review

Yu-Ting Tseng [a,b], Chien-Te Pan [a,b], Shun-Mao Yang [a,c], Sheng-Pin Yu [a,d], Pei-Ming Huang [a,b,*]

Supported by Taiwan Society of Pulmonary and Critical Care Medicine

What is NTM

- Mycobacterial species other than the ***Mycobacterium tuberculosis* complex** (*M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii, M suricattae* and *M. mungi*) and those organisms causing **leprosy** (*M. leprae* and *M. lepromatosis*)



Nontuberculous mycobacterium(NTM) lung disease: an emerging disease entity

Chien et al. Emerg Infect Dis 2014

Prior TB is an important underlying cause of NTM

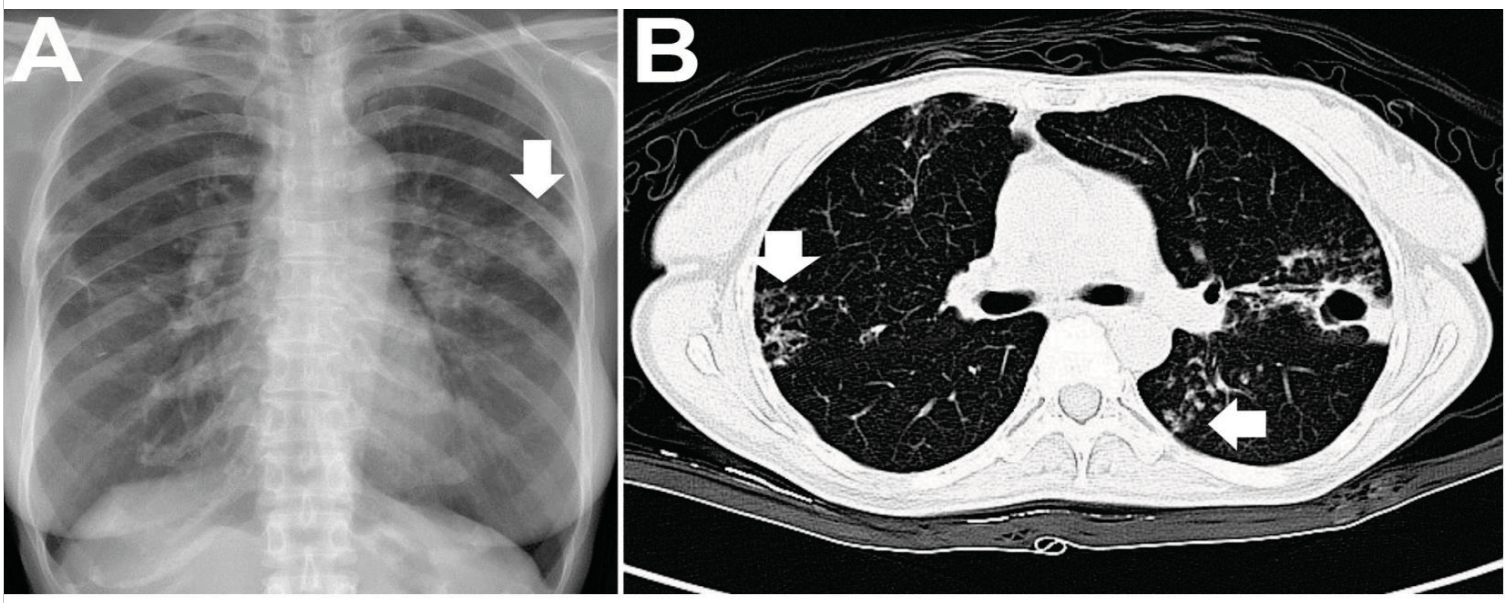
	Country	NTM species	N	Prior TB
Chen LC et al. 2020	Taiwan	*M. chimaera*	28	6 (21.4)
Koh WJ et al. 2011	Korea	*M. abscessus*	145	77 (53.1%)
Costa A et al. 2013	Brazil	MAC, *M. abscessus*, *M. kansasii*	29	22 (75.8%)
Pan SW et al. 2017	Taiwan	MAC	126	23 (18%)

Pan et al. Clin Infect Dis 2017
Chen et al. J Infect 2020
Koh et al. Am J Respir Crit Care Med 2011
Costa et al. PLoS Negl Trop Dis 2013

Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease	
Clinical	Pulmonary or Systemic Symptoms
Radiologic	**Nodular or cavitary opacities** on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules
And	Appropriate exclusion of other diagnoses
Microbiologic	1. Positive culture results from **at least two separate expectorated sputum samples**. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures or 2. Positive culture results from at least one bronchial wash or lavage or 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

Clinical + Radiologic + Microbiologic

Griffith et al. Am J Respir Crit Care Med 2007
Daley et al. Clin Infect Dis 2020

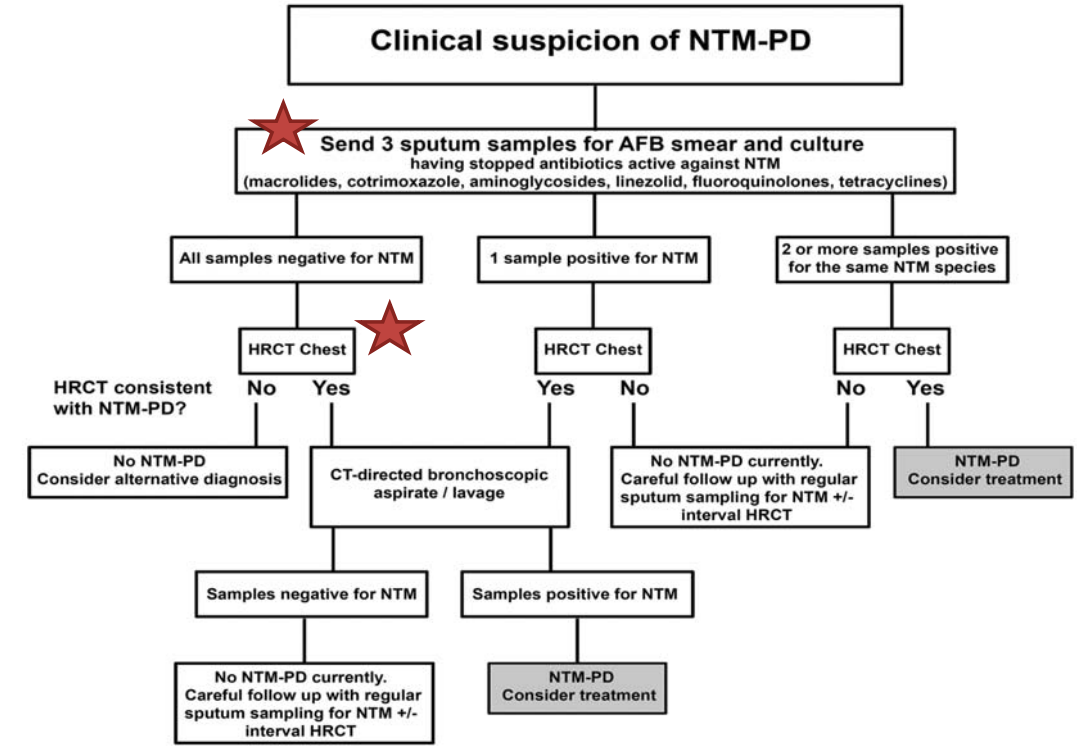


Clinical Characteristics of Patients with a Single Isolation of NTM

Characteristic	Total (n=202)	MAC (n=70)	M. che-abs (n=40)	M. kansasii (n=21)	M. fortuitum (n=71)
Age: median [range]	70 [13 – 99]	71 [32-93]	70 [48– 89]	71 [45 – 99]	68 [13 – 93]
Male	120 (59%)	47 (67.1%)	21 (53%)	16 (76%)	36 (51%)
Number of sputum samples within one year	7.8 ± 3.5	8 ± 3.54	7.8 ± 3.8	7.4 ± 3.2	7.6 ± 3.3
Microbiology follow-up period, months	12.0	14.9	12.7	14.2	8.1
Clinical follow-up period, months	26.2	28.8	26.9	24.8	23.7
Presence of subsequent positive culture	**44 (22%)**	19 (27%)	8 (20%)	5 (24%)	12 (17%)
Diagnosed as NTM pulmonary disease	**8 (4%)**	6 (9%)	1 (3%)	1 (5%)	0

44/202 (22%) single NTM isolation had subsequent cultures of same NTM species
Only 8/202 (4%) developed NTM-LD

Lee et al. Clin Microbiol Infect 2015



懷疑 NTM-PD -> 驗三套痰加CT

Identification of NTM species

- Commercial nucleic acid probes
- PCR restriction-enzyme analysis (PRA)
- Gene sequencing
- MALDI-TOF
- Line probe assay

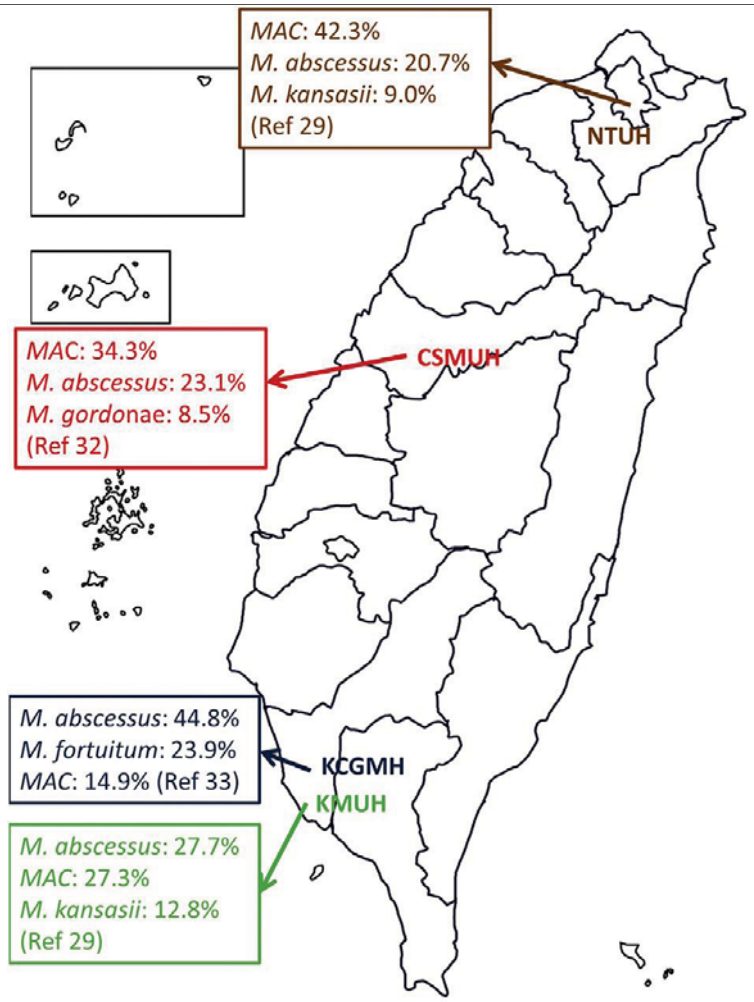
Huang et al. J Formosa Med Assoc 2020

Table 2 NTM isolates that are clinically significant and non-significant.

Significant	Non-significant
1. NTM isolates recovered from sterile sites, such as the blood, pleural effusion, cerebrospinal fluid, soft tissue, and lymphadenopathy. 2. Isolation of NTM species from an immunocompromised host, especially those on corticosteroids and antitumor necrosis factor therapy. 3. Isolates from multiple samples and in large quantities.	1. Isolation of *M. gordonae*, *M. terrae* complex, *M. chelonae*, the *M. mucogenicum* group, *M. botniense*, *M. chlorophenolicum*, *M. aromaticivorans*, M. hodleri, *M. murale*, *M. pallens*, *M. rufum*, *M. rutilum*, *M. litorale*, M. arabiense, M. sediminis, M. paragordonae, *M. cookii*, M. fredericksbergense, and *M. psychrotolerans* from respiratory samples. 2. The *M. fortuitum* group is rarely a respiratory pathogen except in patients with lipoid pneumonia or achalasia. 3. Isolates recovered in single sample and small numbers of colonies.

Significance of NTM varies with species

Huang et al. J Formosa Med Assoc 2020



Northern Taiwan: MAC

Southern Taiwan: *M. abscessus complex* and MAC

Lee et al. J Formosa Med Assoc 2020

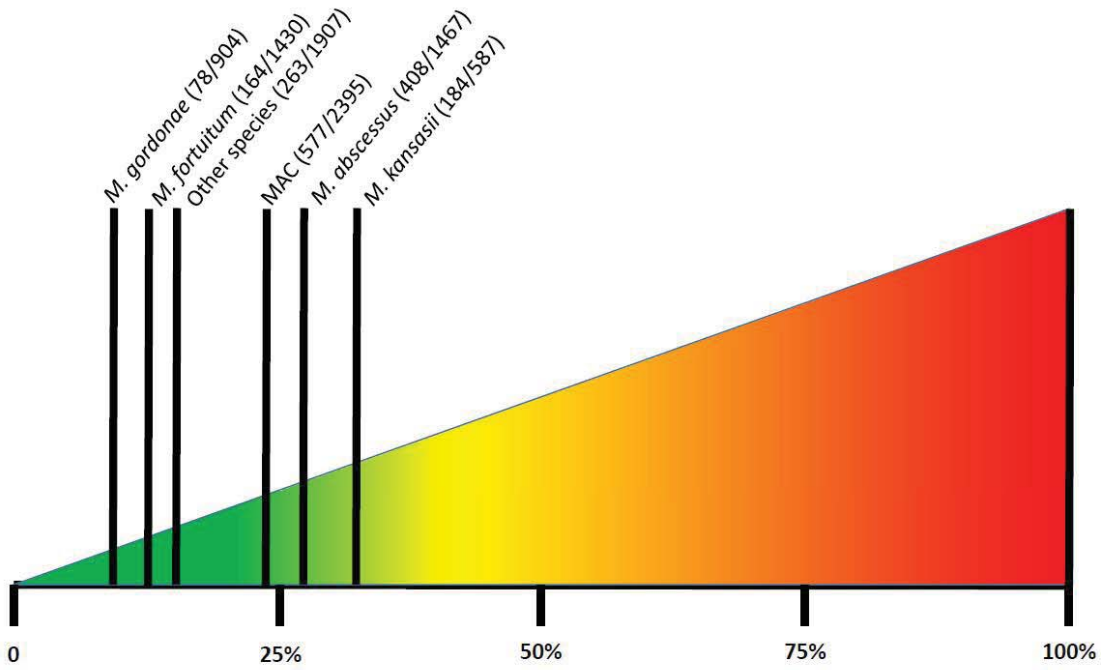


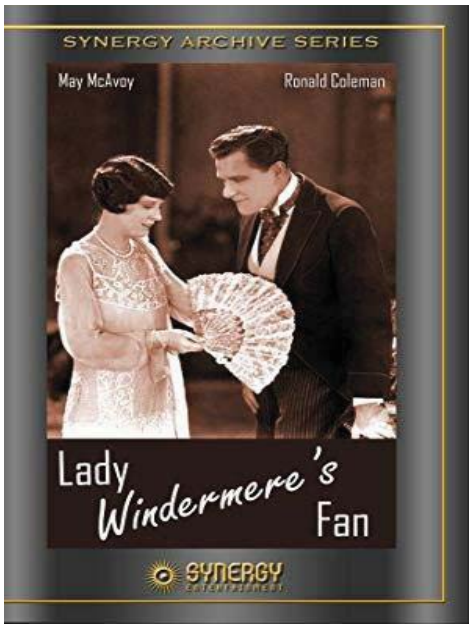
Figure 1 Clinical relevance of nontuberculous mycobacteria (NTM) isolated from respiratory samples in Taiwan. Data were modified from Huang et al.[54]

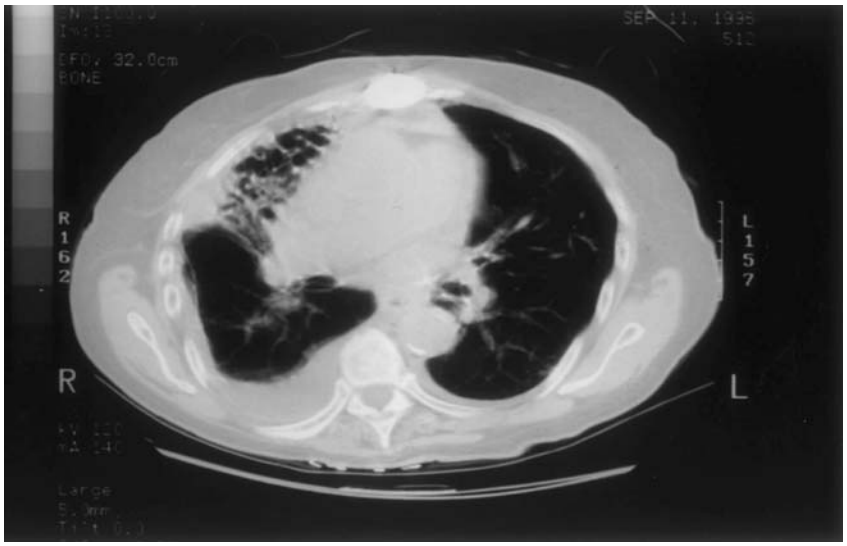
Feng et al. J Formosa Med Assoc 2020

Lady Windermere Syndrome: Middle Lobe Bronchiectasis and *Mycobacterium avium* Complex Infection Due to Voluntary Cough Suppression

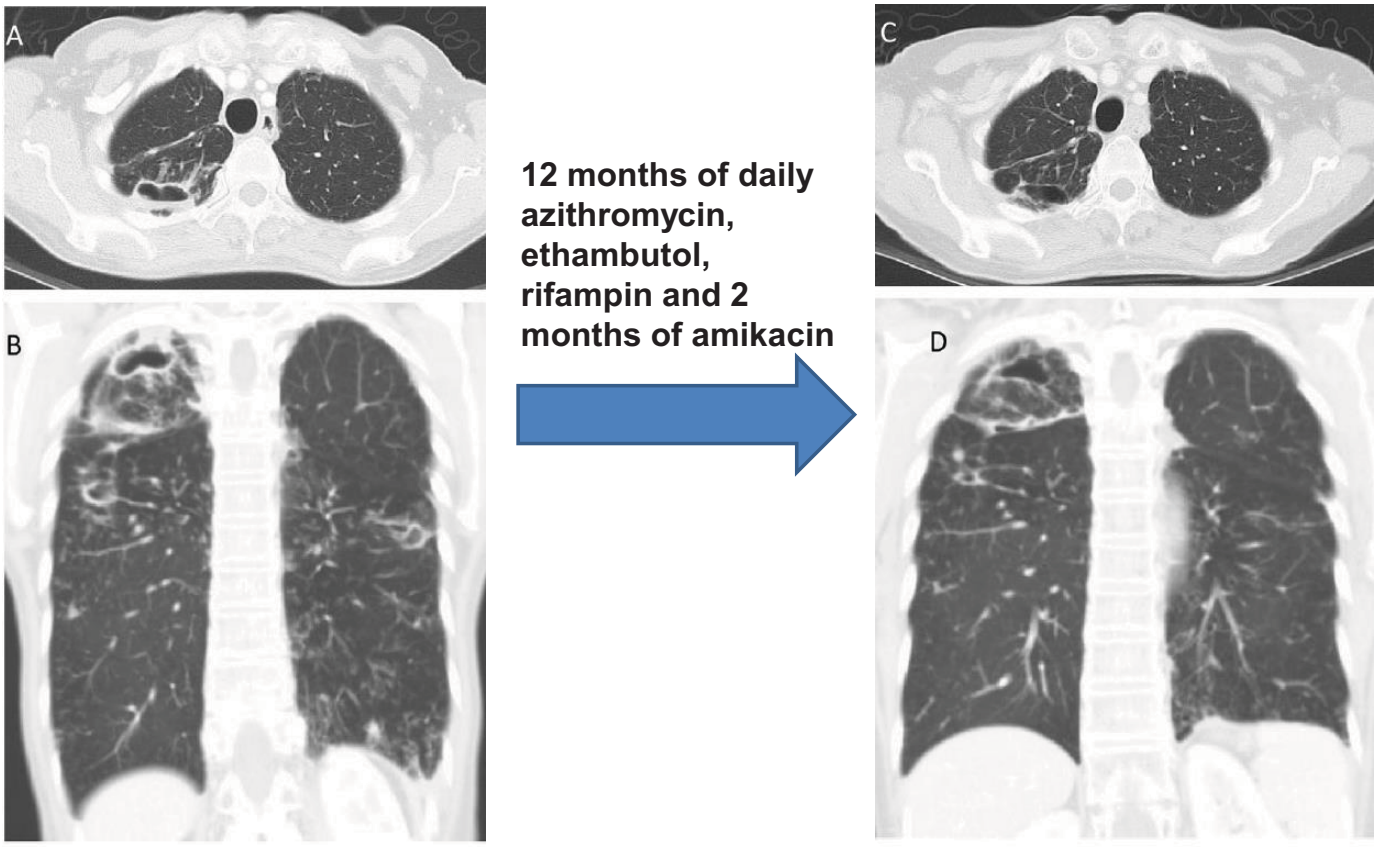
Samjot Singh Dhillon[1] and Chatrchai Watanakunakorn[1,2]

[1]*Department of Internal Medicine, St. Elizabeth Health Center, Youngstown, and* [2]*Northeastern Ohio Universities College of Medicine, Rootstown, Ohio*





MAC-LD



Pan et al. J Formosa Med Assoc 2020

J Antimicrob Chemother 2012; **67**: 810–818
doi:10.1093/jac/dkr578 Advance Access publication 30 January 2012

Journal of Antimicrobial Chemotherapy

Mycobacterium abscessus: a new antibiotic nightmare

Rachid Nessar[1]†, Emmanuelle Cambau[2]†, Jean Marc Reyrat[1]‡, Alan Murray[3,4]† and Brigitte Gicquel[3]*†

Table 1 *In vitro* susceptibilities of *M. abscessus* complex to 15 antimicrobial agents in Taiwan.

	Susceptibility (%)				
	Taiwan			North-east Asia[30–32]	European and American countries[9,33,34,36,37]
	North[12,13]	Central[12,14,15]	South[12]		
Amikacin	95–96	90–95	98	99–100	52–92
Tobramycin	27–100	17	33	NA	NA
Ofloxacin	92	93	83	NA	NA
Ciprofloxacin	3–42	10–22	48	0–57	0–3
Moxifloxacin	8	23	NA	73	NA
Minocycline	61	4–41	45	15–44	0–5
Doxycycline	0–5	0–8	7	7–35	2–5
Cefoxitin	3–56	22–33	45	66–99	0–27
Imipenem	12–21	13–25	45	31–55	0–37
Erythromycin	51	27	17	NA	NA
Clarithromycin	54–79	58–93	43	62–91	57–85
Azithromycin	52	NA	NA	78	85
TMP-SMX[a]	1	8	NA	0–75	NA
Linezolid	32	NA	NA	77–96	29
Tigecycline	NA	97–100	NA	NA	100

[a] TMP-SMX, trimethoprim-sulfamethoxazole; NA, not available.

M. kansasii

- High Virulence
- Clinical presentations resembling pulmonary TB

	No. of respiratory samples or NTM isolates					No. of NTM-PI episodes				
	2010	2011	2012	2013	2014	2010	2011	2012	2013	2014
Northern Taiwan										
Respiratory samples	21,966	23,158	37,254	28,165	26,050	—	—	—	—	—
NTM isolates (Total)	1,193	1,348	2,093	2,054	1,739	158	157	204	169	119
M. abscessus	189	257	472	364	395	25	42	34	31	33
MAC	381	488	771	1051	741	60	64	71	84	58
M. kansasii	68	102	155	106	161	18	12	19	12	11
Others	555	501	695	533	442	55	39	80	42	17
Sothern Taiwan										
Respiratory samples	18,691	20,472	34,517	31,033	34,838	—	—	—	—	—
NTM isolates (Total)	606	968	1,821	1,230	1,728	87	114	230	172	253
M. abscessus	147	274	411	318	347	28	46	60	51	58
MAC	157	207	399	241	368	31	43	59	46	61
M. kansasii	15	55	147	108	232	3	10	25	17	57
Others	287	432	864	563	781	25	45	86	58	77

An emerging disease entity in Southern Taiwan?

Huang et al. J Formosa Med Assoc 2020 69

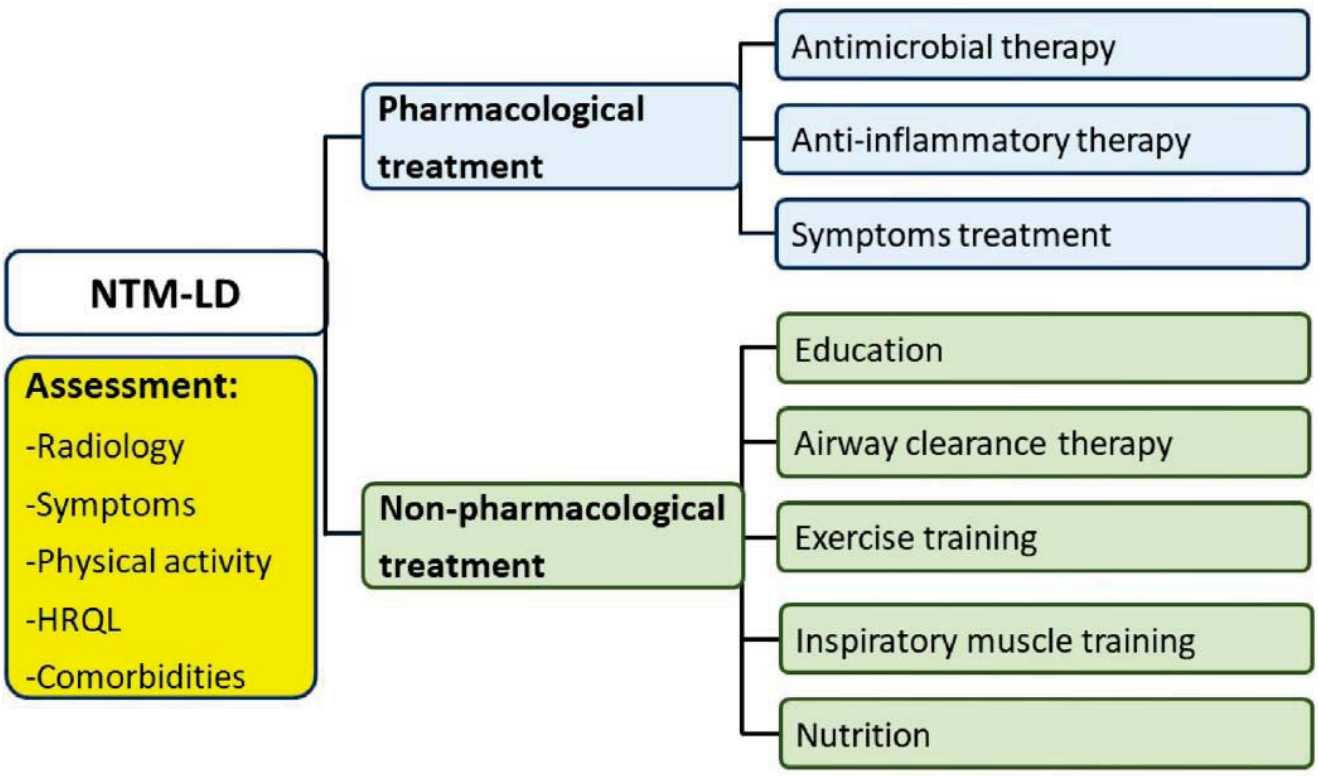


Figure 1 Comprehensive treatment of NTM-LD.

Lan et al. J Formos Med Assoc 2020 70

Therapies	Items	Indications	Benefits
Education	Knowledge about disease, Self-care technique, Pharmacological treatment , Non-pharmacological treatment ,Smoking cessation, Hospice care	All patients	Improve self-management
Airway Clearance Therapy	Active cycle of breathing techniques (ACBT), Autogenic drainage (AD) ,Forced expiration technique (FET), Mmanual techniques (MTs), Postural drainage (PD),Positive expiratory pressure (PEP), Oscillating positive expiratory pressure (OPEP),High frequency chest wall oscillation (HFCWO)	- Copious secretions - Respiratory infection with retained secretions - Acute atelectasis	- Increase amount of sputum expectorated - Improve symptoms (cough, dyspnea - Improve HRQL - Decrease RV, FRC, and TLC
Exercise training	Bike, Treadmill, Walking, Swimming, Resistance training (with hand weights or bands)	- Poor exercise capacity - Poor HRQL - Persistent dyspnea	- Improve exercise capacity - Improve HRQL - Improve symptoms (dyspnea, fatigue) - Decrease acute exacerbation
Inspiratory muscle training	Inspiratory muscle training device	Low maximal inspiratory pressure and maximal expiratory pressure	- Increase respiratory muscle strength - Improve exercise capacity - Improve HRQL - Decrease dyspnea
Nutrition	High-calorie intake/ High protein content, Fruits and vegetables, Vitamin and mineral supplements, Oral nutritional supplements	Malnutrition (BMI< <20 kg/m², serum albumin <3.5 g/dL)	Increased muscle strength and HRQL (with pulmonary rehabilitation program)

Lan et al. J Formos Med Assoc 2020

Surgical Management of NTM-LD

Surgical indication

- Complicated cases (a failed sputum culture conversion after 6 months of therapy)
- Significant symptoms (hemoptysis, persisting bronchiectasis)
- Localized disease (destroyed lung)
- Cavitary lesions (regardless of achieving negative sputum conversion in response to antimicrobial therapy)
- Suspicion of cancer

Tseng et al. J Formos Med Assoc 2020

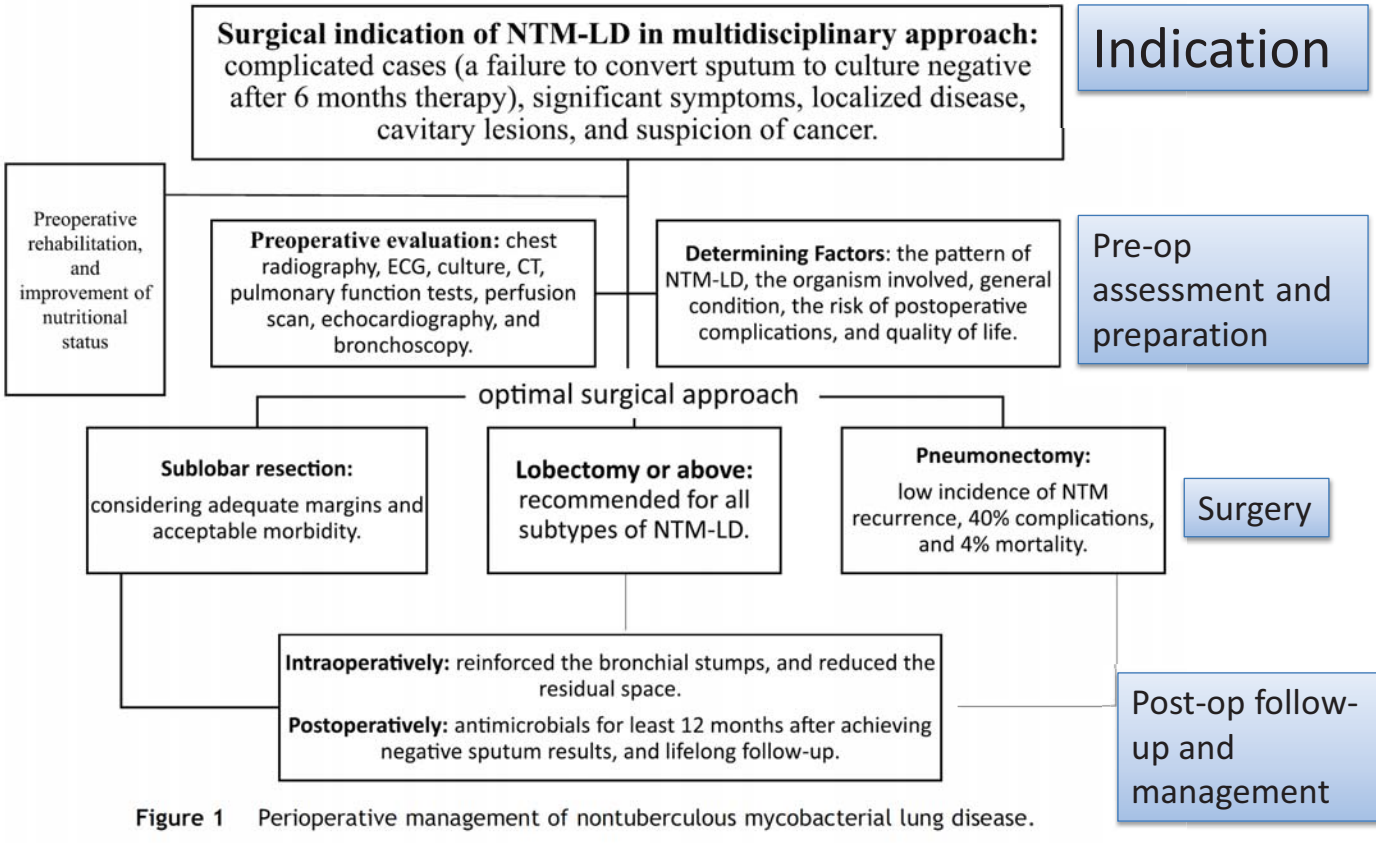


Figure 1 Perioperative management of nontuberculous mycobacterial lung disease.

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Table 2 Host factors associated with nontuberculous mycobacteria–lung disease (NTM-LD).

Mechanism	Dysfunction type	Disease representative	Population size, general	Population size, Taiwan	Association with NTM-LD	Treatable/ controllable?
Defense defect of pulmonary physiology and clearance	Ciliary defect	Primary ciliary dyskinesia	12,000 to 17,000 in Norway and Japan[39,40]; 3% in bronchiectasis in the the United States[41]	Rare	NTM isolation has been reported as 1.1–1.9%[41,43]	No
		Bronchiectasis	Prevalence 94.8 per 100,000 population[44]	Prevalence 130 per 100,000 population[45]	1.7%–8.3% with NTM isolation and 0.48%–2.3% met microbiologically defined NTM-LD,[47,48] OR of 2.14[67]	Controllable for the cause and secondary infection
	Inspissated secretion	Cystic fibrosis	30,000 people in the United States[49]	Very rare	3%–13% NTM-LD has been reported in patients with CF[53,54]	No
	Structural lung change	Cartilage and elastin deficiency in airway	Rare	Rare	No adequate data	No
		Bronchiectasis	As above			
		COPD	Common. Prevalence 9.9% in United Kingdom,[64] and 14.3% in Latin America.[65]	Common. Prevalence 6.1% in Taiwan[63]	Coexistence of 14% –39%[15,30]; OR = 1.17 –15.7[62,66,67]	Controllable
		Alpha-1 antitrypsin deficiency	3–5 in 1500 individuals with European ancestry	Rare	No large study. Might be compatible with COPD	Controllable
	Macrophage dysfunction	Pulmonary alveolar proteinosis	40 cases per million[73]	Rare	MAC has been isolated from 8 among 19 patients with PAP79	Controllable

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Mechanisms	Dysfunction type	Disease representative	Population size, general	Population size, Taiwan	Association with NTM-LD
Immunosuppression	Immune deficiency in lung	Inhaled corticosteroids	Common drug	Common drug	OR = 1.86-2.74
	Systemic immune deficiency	Anti-TNF-α therapy	Not uncommon; approximately 0.4%	Not uncommon	OR= 2.19

Identify correctable and manageable factors associated with NTM-LD

Shu et al. J Formos Med Assoc 2020[75]

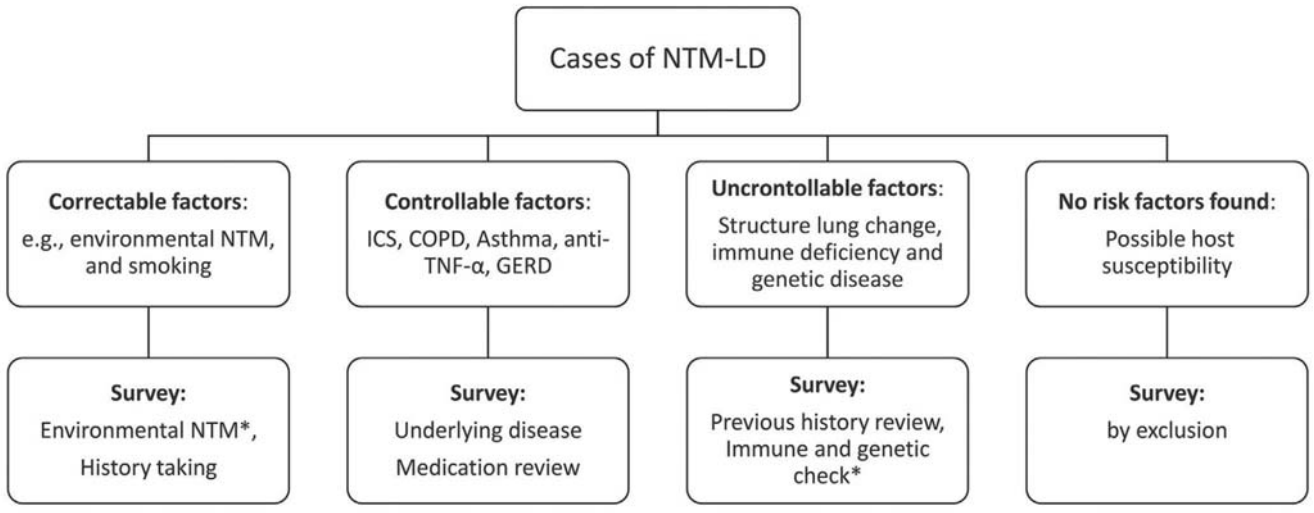
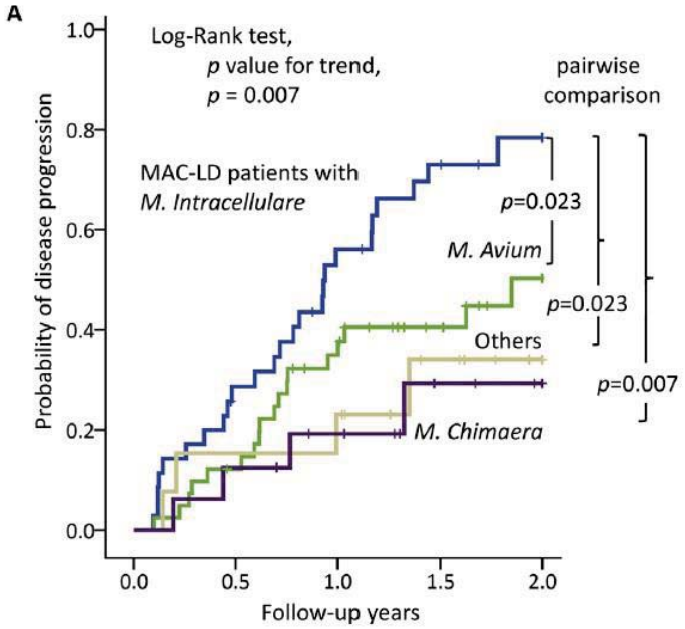


Figure 1 Risk survey for nontuberculous mycobacterial lung disease (NTM-LD). Asterisks indicate not included in general survey but available for some laboratories. Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastro-esophageal reflux disease; ICS, inhaled corticosteroid; NTM, nontuberculous mycobacteria; TNF-α, tumor necrosis factor-alpha.

Shu et al. J Formos Med Assoc 2020[76]

MAC subspecies



105 MAC isolates from MAC-LD patients
35 (33%) *M. intracellulare*
41 (39%) *M. avium*
16 (15%) *M. chimaera*
13 (12%) other species

Risk of disease progression lower with *M. chimaera*

Pan, Shu et al. Clin Microbiol Infect 2020

ORIGINAL ARTICLE BACTERIOLOGY

Extrapulmonary infections caused by a dominant strain of *Mycobacterium massiliense* (*Mycobacterium abscessus subspecies bolletii*)

TABLE 3. TREATMENT RESPONSES FOR PATIENTS WITH *MYCOBACTERIUM ABSCESSUS* AND *MYCOBACTERIUM MASSILIENSE* LUNG DISEASE

	M. abscessus (*n* = 24)	*M. massiliense* (*n* = 33)	*P* Value
Symptomatic response			0.040
Improved	18 (75%)	32 (97%)	
Unchanged	4 (17%)	1 (3%)	
Worsened	2 (8%)	—	
Radiographic response on HRCT			0.003
Improved	10 (42%)	27 (82%)	
Unchanged	7 (29%)	5 (15%)	
Worsened	7 (29%)	1 (3%)	
Microbiologic response			<0.001
Initial sputum conversion and maintenance of conversion	6 (25%)	29 (88%)	
Initial sputum conversion, with sputum relapse	4 (17%)	3 (9%)	
Failure to sputum conversion	14 (58%)	1 (3%)	

Subspecies of *M. abscessus* complex are associated with different clinical outcome

Cheng et al. Clin Microbiol Infect 2012
Koh et al. Am J Respir Crit Care Med 2011

Table 4 Presence of inducible macrolide resistance based on *erm* gene types in rapidly growing mycobacteria.

Clarithromycin MIC reports beyond 5-day incubation	Functional Resistant	Nonfunctional Susceptible
Species or subspecies/ gene types	*M. goodie/erm(38)* *M. smegmatis/ erm*(38) *M. fortuitum/ erm*(39) *M. houstonense/ erm*(39) *M. porcinum/ erm*(39) *M. neworleansense/ erm*(39) *M. mageritense/ erm*(40) *M. wolinskyi/ erm*(40) *M. abscessus*subsp. *abscessus/erm*(41) *M. abscessus*subsp. *bolletii/erm*(41)	*M. abscessus* subsp. *massiliense* *M. chelonae* *M. immunogenum* *M. mucogenicum* group *M. peregrinum* *M. senegalense*

Abbreviations: see Table 1.

Table 3 Summary of the associations between *in vitro* susceptibility and clinical outcome in patients with NTM infection.

	Antimicrobials with *in vitro* resistance	Treatment outcome
M. avium complex infection	Clarithrimycin and amikacin	Unfavorable
M. kansasii infection	Rifampicin	
M. abscessus lung disease	Clarithromycin	
Extrapulmonary *M. abscessus* infection	Cefoxitin, amikacin, and cotrimoxazole	

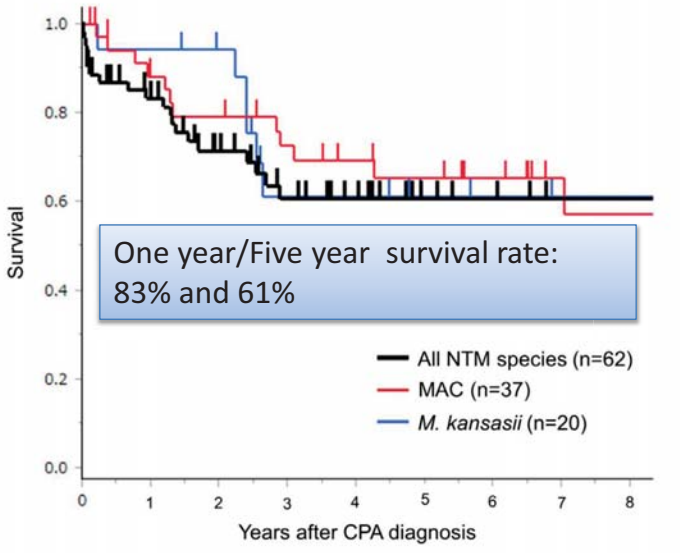
From subspecies to drug susceptibility to clinical outcome

Huang et al. J Formos Med Assoc 2020

Post-TB/NTM/Aspergillus Colonization

Table 1 – Patient characteristics (n=62).

Age, years		69.5	(42–87)
Sex, female/male		24/38	
Smoking, never/former or current		24/38	
Underlying disease			
	Old pulmonary tuberculosis	18	(29%)
	COPD	24	(39%)
	Diabetes mellitus	8	(13%)
	Interstitial lung disease	14	(23%)
	Asthma	7	(12%)
	Cancer	13	(21%)
	Collagen disease	11	(18%)
Use of systemic corticosteroids		16	(26%)
Mycobacterium species			
	Mycobacterium avium	23	(37%)
	Mycobacterium intracellulare	14	(23%)
	Mycobacterium kansasii	20	(32%)
	Mycobacterium szulgai	3	(4.8%)
	Mycobacterium abscessus	1	(1.6%)
	Mycobacterium fortuitum	1	(1.6%)



Naito et al. Respir Invest 2018

Thanks for Your Attention!