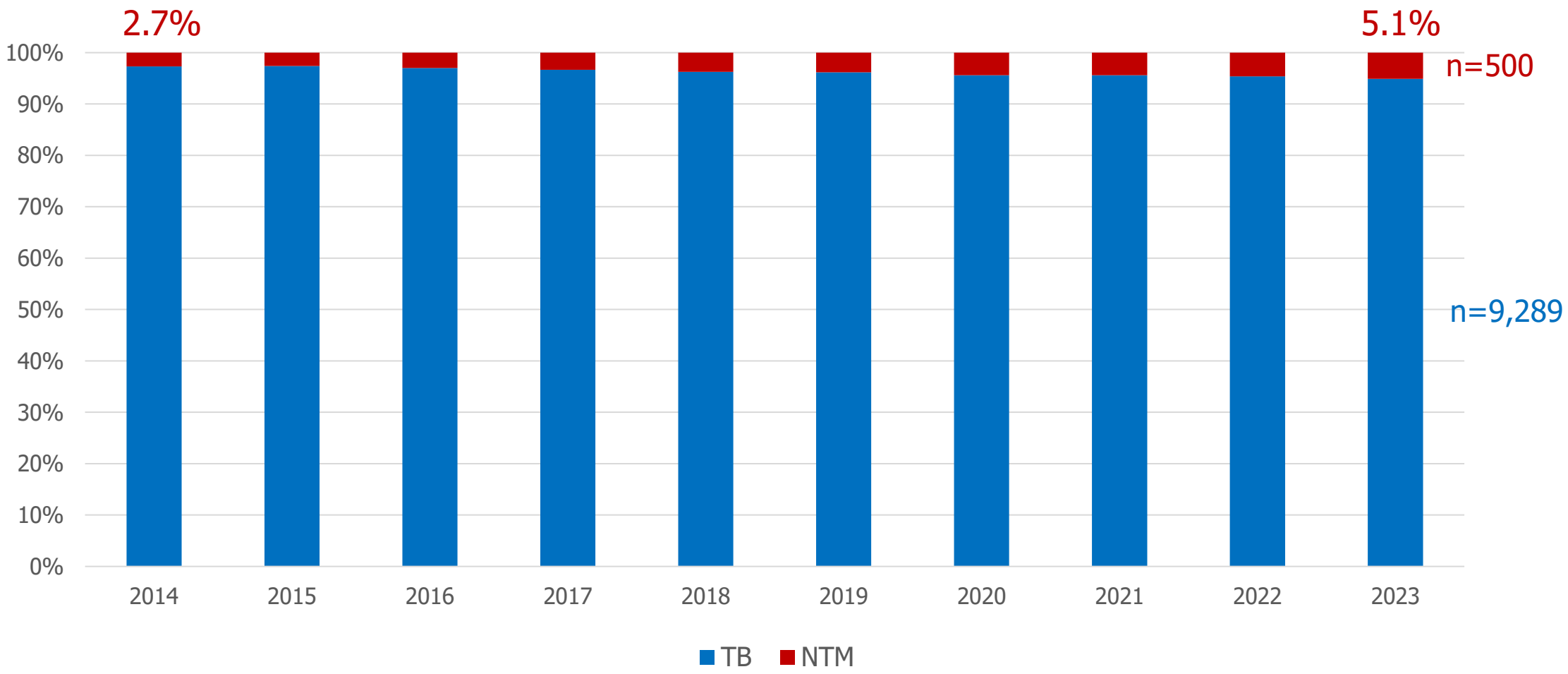
Respiratory Review of 2024

TB/NTM

2024.4.13

대한결핵 및 호흡기학회 춘계학술대회
부산대학교병원 호흡기내과 목정하

Publications (PubMed)



Tuberculosis

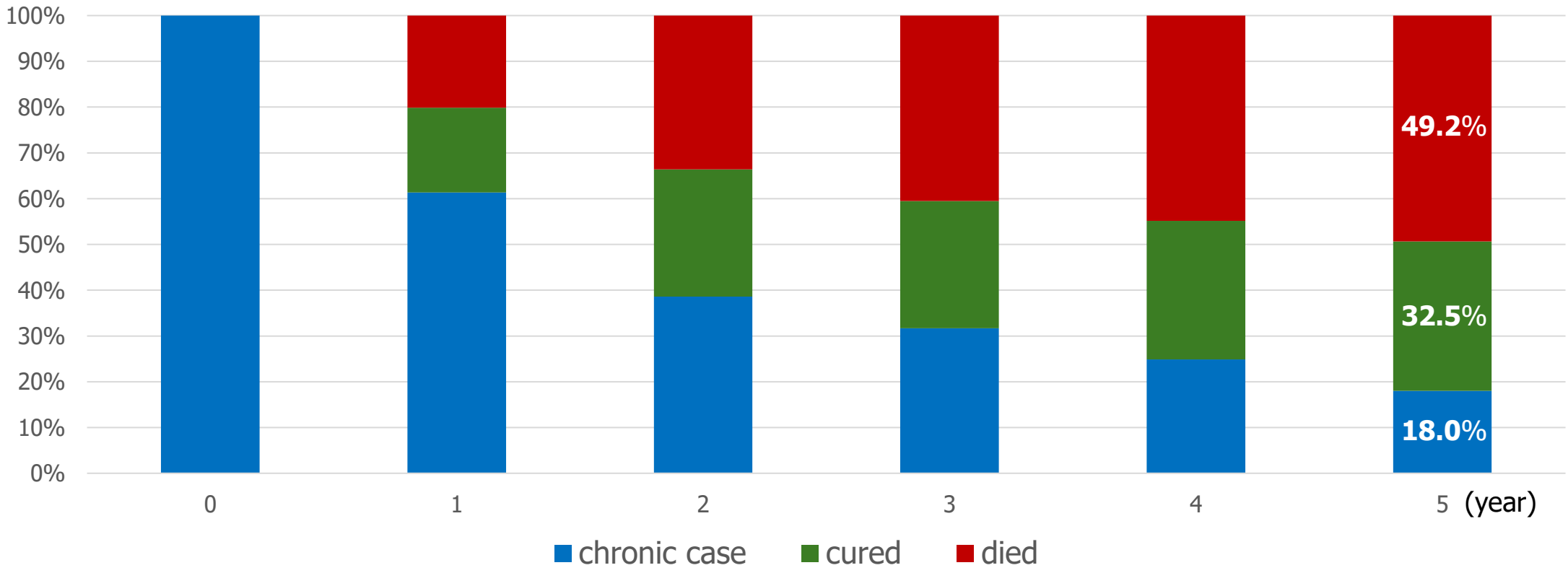
The natural history of untreated pulmonary tuberculosis in adults: a systematic review and meta-analysis

Bianca Sossen, Alexandra S Richards*, Torben Heinsohn, Beatrice Frascella, Federica Balzarini, Aurea Oradini-Alacreu, Anna Odone, Ewelina Rogozinska, Brit Häcker, Frank Cobelens, Katharina Kranzer, Rein M G J Houben†, Hanif Esmail†*

Lancet Respir Med. 2023;11:367-79.

In the previous observation,

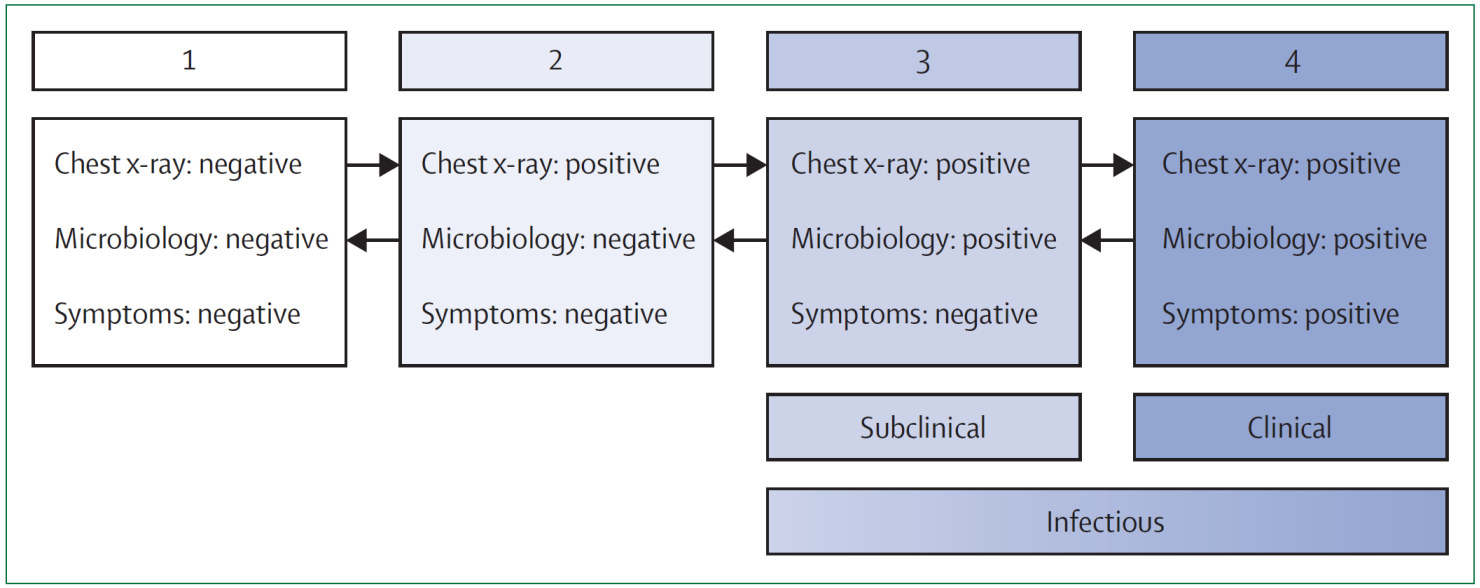
AFB smear (+) PTB patients in India (1961-1968) [n=126]



Bull World Health Organ. 1974;51:473-88.

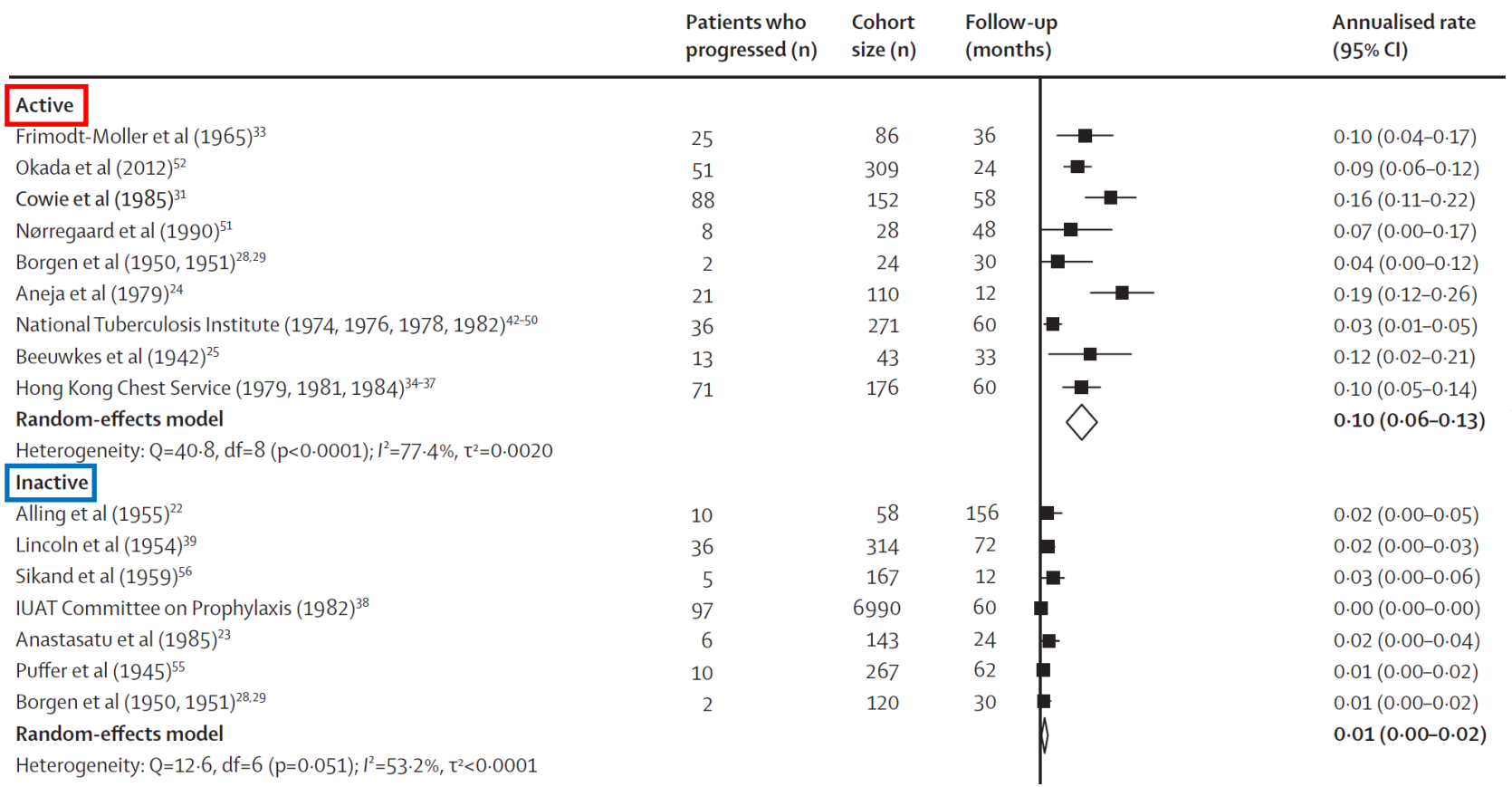
Natural history of untreated PTB

- Meta-analysis of individuals with untreated PTB (1900-1960, n=139,063)
- Microbiologically negative → positive disease [progression]
- Microbiologically positive → undetectable disease [regression]



Lancet Respir Med. 2023;11:367–79.

Microbiologically progression



	Patients who progressed (n)	Cohort size (n)	Follow-up (months)	Annualised rate (95% CI)
Active				
Frimodt-Moller et al (1965)[33]	25	86	36	0·10 (0·04–0·17)
Okada et al (2012)[52]	51	309	24	0·09 (0·06–0·12)
Cowie et al (1985)[31]	88	152	58	0·16 (0·11–0·22)
Nørregaard et al (1990)[51]	8	28	48	0·07 (0·00–0·17)
Borgen et al (1950, 1951)[28,29]	2	24	30	0·04 (0·00–0·12)
Aneja et al (1979)[24]	21	110	12	0·19 (0·12–0·26)
National Tuberculosis Institute (1974, 1976, 1978, 1982)[42–50]	36	271	60	0·03 (0·01–0·05)
Beeuwkes et al (1942)[25]	13	43	33	0·12 (0·02–0·21)
Hong Kong Chest Service (1979, 1981, 1984)[34–37]	71	176	60	0·10 (0·05–0·14)
Random-effects model				**0·10 (0·06–0·13)**
Heterogeneity: Q=40·8, df=8 (p<0·0001); I^2=77·4%, τ^2=0·0020				
Inactive				
Alling et al (1955)[22]	10	58	156	0·02 (0·00–0·05)
Lincoln et al (1954)[39]	36	314	72	0·02 (0·00–0·03)
Sikand et al (1959)[56]	5	167	12	0·03 (0·00–0·06)
IUAT Committee on Prophylaxis (1982)[38]	97	6990	60	0·00 (0·00–0·00)
Anastasatu et al (1985)[23]	6	143	24	0·02 (0·00–0·04)
Puffer et al (1945)[55]	10	267	62	0·01 (0·00–0·02)
Borgen et al (1950, 1951)[28,29]	2	120	30	0·01 (0·00–0·02)
Random-effects model				**0·01 (0·00–0·02)**
Heterogeneity: Q=12·6, df=6 (p=0·051); I^2=53·2%, τ^2<0·0001				

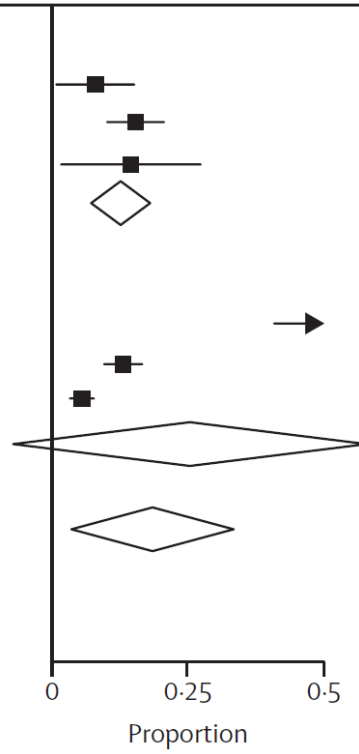
Annual 10%
(26%/3yr)

Annual 1%
(3%/3yr)

Lancet Respir Med. 2023;11:367–79.

Microbiologically regression

	Patients who regressed (n)	Cohort size (n)	Follow-up (months)	Annualised rate (95% CI)
Prospective				
Marshall et al (1948)[41]	2	52	6	0·08 (0·00–0·15)
National Tuberculosis Institute (1974, 1976, 1978, 1982)[42–50]	70	178	36	0·15 (0·10–0·20)
Beeuwkes et al (1942)[25]	10	28	33	0·14 (0·01–0·27)
Random-effects model				**0·12 (0·07–0·18)**
Heterogeneity: Q=2·7, df=2 (p=0·25); I^2=35·1%, τ^2=0·0008				
Retrospective				
Manser (1953)[40]	15	40	6	0·60 (0·45–0·75)
Downes (1938)[32]	171	342	60	0·13 (0·09–0·16)
Puffer et al (1945)[55]	92	384	62	0·05 (0·03–0·07)
Random-effects model				**0·25 (–0·08 to 0·58)**
Heterogeneity: Q=58·3, df=2 (p<0·0001); I^2=99·5%, τ^2=0·082				
Random-effects model for all studies				**0·18 (0·03–0·33)**
Heterogeneity: Q=65·1, df=5 (p<0·0001); I^2=98·1%, τ^2=0·033				
Test for subgroup differences: Q_M=0·5, df=1 (p=0·46)				



Annual 12%
(33%/3yr)

Lancet Respir Med. 2023;11:367–79.

Natural history of untreated PTB

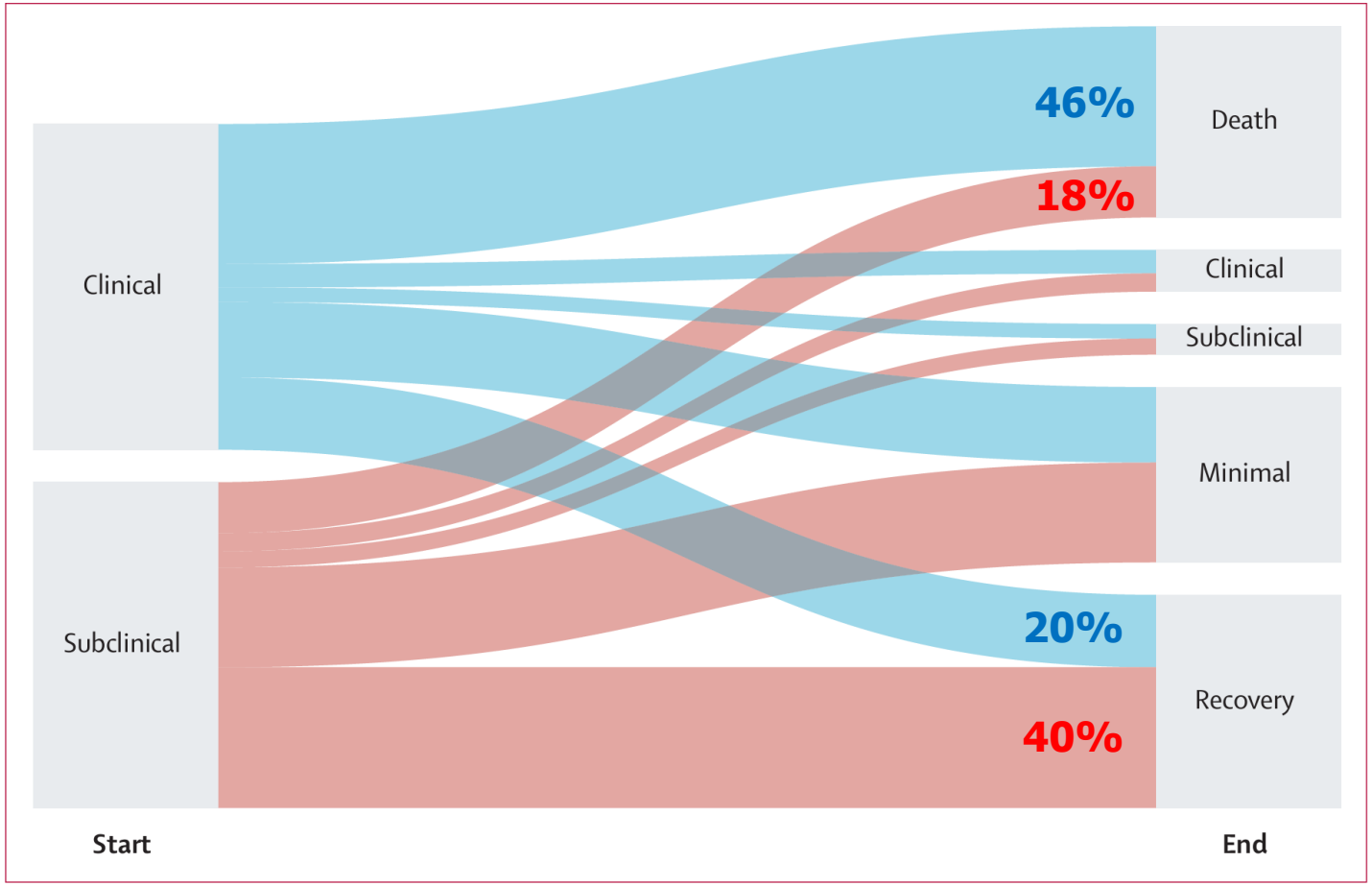


Figure 3: Final state after 5 years in people starting with subclinical or clinical disease

Lancet Glob Health. 2023;11:e684-92.

Long-Term Mortality of Tuberculosis Survivors in Korea: A Population-based Longitudinal Study

Hayoung Choi,[1] Kyungdo Han,[2] Jin-Hyung Jung,[3] Sang Hyun Park,[3] Sang Hyuk Kim,[1] Hyung Koo Kang,[4] Jang Won Sohn,[5] Dong Wook Shin,[6,7,8,a] and Hyun Lee[5,a]

Clin Infect Dis. 2023;76:e973-e981.

Long-term mortality of TB survivors

- Retrospective study
- National Health Insurance Service (NHIS) database of Korea
- PTB or EPTB patients aged ≥20 years (2010-2017)
- TB survivors (n=82,098) vs. controls (n=82,098) [1:1 age- and sex-matched]

→ Death at least 1 year after TB diagnosis (median F/U duration, 3.7 years)

Long-term mortality of TB survivors

Table 2. Incidence Rate and Risk of Mortality in TB Survivors Versus Matched Controls

			No. at Risk	No. of Deaths	Follow-up Duration (PY)	IR (/1000 PY)	Hazard Ratio (95% CI)			
							Unadjusted	Model 1	Model 2	Model 3
Overall	Matched controls		82 098	2738	312 552	8.8	Reference	Reference	Reference	Reference
	TB survivors		82 098	5549	304 971	18.2	2.08 (1.99–2.18)	1.86 (1.78–1.95)	1.55 (1.47–1.62)	1.62 (1.54–1.70)
Age group, y	20–29	Control	4328	7	19 160	0.4	Reference	Reference	Reference	Reference
		TB	4328	9	19 155	0.5	1.29 (.48–3.46)	1.17 (.44–3.14)	1.05 (.39–2.83)	1.11 (.41–2.98)
	30–39	Control	9089	23	38 043	0.6	Reference	Reference	Reference	Reference
		TB	9089	48	37 960	1.3	2.09 (1.27–3.44)	1.82 (1.11–2.99)	1.62 (.98–2.66)	1.71 (1.04–2.80)
	40–49	Control	14 637	57	57 904	1.0	Reference	Reference	Reference	Reference
		TB	14 637	212	57 463	3.7	3.75 (2.80–5.03)	3.13 (2.34–4.20)	2.64 (1.97–3.54)	2.80 (2.09–3.76)
	50–59	Control	18 130	198	69 221	2.9	Reference	Reference	Reference	Reference
		TB	18 130	669	68 047	9.8	3.44 (2.94–4.03)	2.83 (2.41–3.32)	2.31 (1.97–2.71)	2.44 (2.08–2.86)
	60–69	Control	16 214	464	60 593	7.7	Reference	Reference	Reference	Reference
		TB	16 214	1272	58 375	21.8	2.86 (2.57–3.18)	2.47 (2.22–2.75)	2.01 (1.81–2.24)	2.10 (1.88–2.34)
	70–79	Control	16 096	1400	57 645	24.3	Reference	Reference	Reference	Reference
		TB	16 096	2511	54 605	46.0	1.91 (1.76–2.03)	1.68 (1.58–1.80)	1.40 (1.31–1.50)	1.45 (1.35–1.55)
	≥ 80	Control	3604	589	9986	59.0	Reference	Reference	Reference	Reference
		TB	3604	828	9366	88.4	1.51 (1.36–1.68)	1.38 (1.24–1.53)	1.16 (1.05–1.29)	1.22 (1.10–1.36)
Sex	Male	Control	46 755	1823	175 380	10.4	Reference	Reference	Reference	Reference
		TB	46 755	3979	169 469	23.5	2.26 (2.14–2.39)	2.01 (1.89–2.12)	1.66 (1.57–1.76)	1.73 (1.63–1.84)
	Female	Control	35 343	915	137 172	6.7	Reference	Reference	Reference	Reference
		TB	35 343	1570	135 502	11.6	1.74 (1.60–1.89)	1.56 (1.46–1.72)	1.33 (1.22–1.44)	1.40 (1.28–1.52)

Data are presented as numbers or ratios with 95% CI, as appropriate. Model 1 was adjusted for age, sex, body mass index (continuous variable), smoking pack-years (continuous variable), alcohol consumption, regular exercise, income level, and residential area. Model 2 was adjusted for the Charlson Comorbidity Index (continuous variable) in addition to the variables included in model 1. Model 3 was adjusted for comorbidities (diabetes mellitus, hypertension, dyslipidemia, asthma, chronic obstructive pulmonary disease, bronchiectasis, ischemic heart disease, myocardial infarction, congestive heart failure, stroke, dementia, solid cancer, hematologic malignancy, and chronic kidney disease/end-stage renal disease), in addition to the variables included in model 1.

Clin Infect Dis. 2023;76:e973-e981.

Long-term mortality of TB survivors

Table 3. Risk Factors for Long-term Mortality in TB Survivors

		No. at Risk (N= 82 098)	No. of Deaths	Follow-up Duration (PY)	IR (/1000 PY)	Hazard Ratio (95% CI)		
						Unadjusted	Model 1	Model 2
Type of TB	Extrapulmonary TB	11 054	359	42 722	8.4	Reference	Reference	Reference
	Pulmonary TB	68 801	5054	252 764	20.0	2.38 (2.14–2.65)	1.30 (1.17–1.45)	1.24 (1.11–1.38)
	Pulmonary and extrapulmonary TB	1561	73	6934	10.5	1.25 (.97–1.61)	1.04 (.81–1.33)	0.99 (.77–1.27)
	Miliary or disseminated TB	682	63	2551	24.7	2.95 (2.26–3.86)	1.33 (1.01–1.73)	1.27 (.97–1.67)
Sex	Female	35 343	1570	135 502	11.6	Reference	Reference	Reference
	Male	46 755	3979	169 469	23.5	2.03 (1.91–2.15)	2.33 (2.18–2.50)	2.31 (2.16–2.47)
Age group, y	20–29	4328	9	19 155	0.5	0.13 (.07–.25)	0.59 (.30–1.19)	0.51 (.26–1.02)
	30–39	9089	48	37 960	1.3	0.34 (.25–.47)	0.79 (.57–1.10)	0.73 (.52–1.01)
	40–49	14 637	212	57 463	3.7	Reference	Reference	Reference
	50–59	18 130	669	68 047	9.8	2.67 (2.29–3.12)	1.07 (.89–1.28)	1.13 (.94–1.36)
	60–69	16 214	1272	58 375	21.8	5.93 (5.13–6.86)	1.01 (.80–1.29)	1.09 (.86–1.39)
	70–79	16 096	2511	54 605	46.0	12.63 (10.98–14.54)	1.09 (.80–1.50)	1.19 (.86–1.63)
	≥ 80	3604	828	9366	88.4	24.83 (21.35–28.88)	1.21(.82–1.79)	1.30 (.88–1.92)
Body mass index, kg/m^2		82 098	…	…	…	0.94 (.93–.943)	0.91 (.906–.92)	0.91 (.90–.92)
Smoking pack-years		82 098	…	…	…	1.017 (1.016–1.019)	1.005 (1.004–1.007)	1.005 (1.004–1.006)
Alcohol consumption	None	46 938	3722	173 933	21.4	Reference	Reference	Reference
	Mild	27 490	1262	102 871	12.3	0.57 (.54–.61)	0.87 (.81–.93)	0.88 (.83–.95)
	Heavy	7670	565	28 167	20.1	0.94 (.86–1.03)	1.10 (.997–1.21)	1.12 (1.01–1.23)
Regular exercise	No	68 014	4708	254 294	18.5	Reference	Reference	Reference
	Yes	14 084	841	50 677	16.6	0.90 (.83–.97)	0.82 (.76–.89)	0.82 (.76–.88)
Income level	Quintile 1 (lowest)	15 232	1142	55 508	20.6	0.94 (.87–1.01)	1.27 (1.17–1.37)	1.27 (1.18–1.37)
	Quintile 2	12 929	762	48 643	15.7	0.71 (.65–.78)	1.24 (1.14–1.35)	1.24 (1.14–1.36)
	Quintile 3	15 218	854	57 332	14.9	0.68 (.62–.74)	1.12 (1.03–1.21)	1.13 (1.04–1.23)
	Quintile 4	17 941	1123	67 541	16.6	0.76 (.70–.82)	1.04 (.96–1.12)	1.04 (.96–1.12)
	Quintile 5	20 778	1668	75 946	22.0	Reference	Reference	Reference
Residential area	Metropolitan	36 444	2011	137 786	14.6	Reference	Reference	Reference
	Other areas	45 654	3538	167 185	21.2	1.45 (1.37–1.53)	1.10 (1.04–1.16)	1.09 (1.03–1.16)
Charlson Comorbidity Index		82 098	…	…	…	1.30 (1.29–1.32)	1.15 (1.14–1.17)	…

Risk factors for long-term mortality in TB survivors

- Male sex (aHR 2.31)
- Smoking pack-years (aHR 1.01)
- Heavy alcohol consumption (aHR 1.12)
- Lowest income (aHR 1.27)
- Non-metropolitan residence (aHR 1.09)
- Higher CCI (aHR 1.15)

Clin Infect Dis. 2023;76:e973-e981.

Long-term mortality of TB survivors

Potential mechanisms on high long-term mortality in TB survivors

- Higher rates of cardiovascular mortality

  Cell-mediated immune responses against *M. tuberculosis* → atherogenesis

- Higher rates of respiratory diseases (such as COPD)

  Regardless of smoking status

- Weight loss during TB course

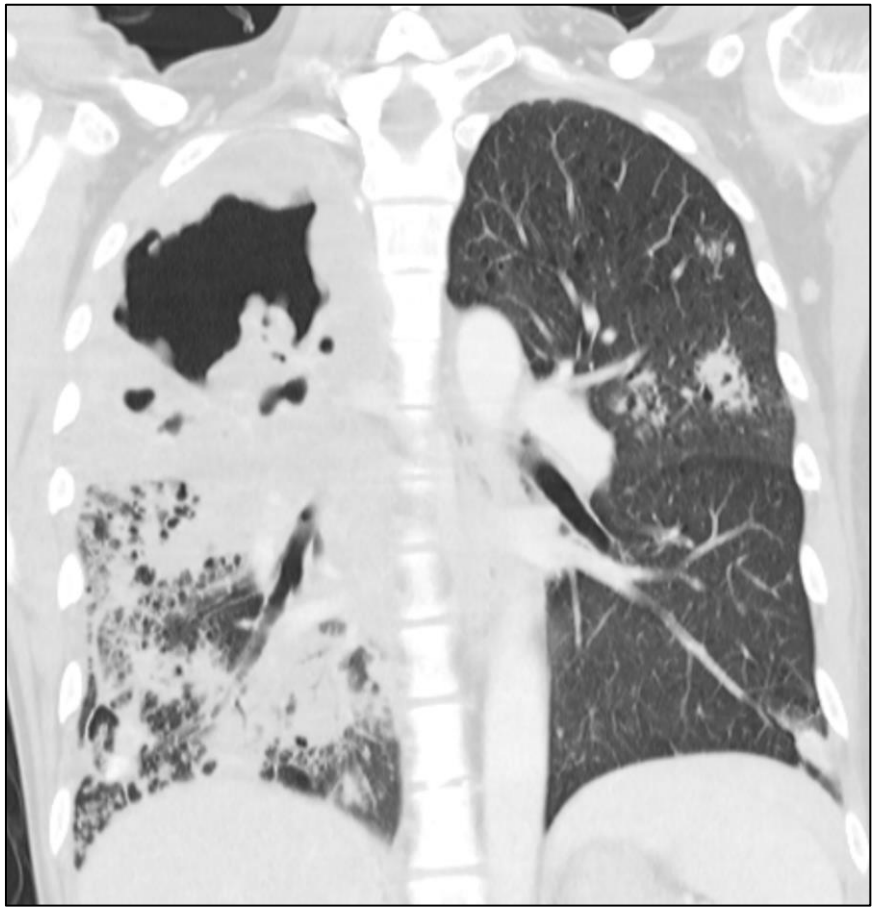
Post-tuberculosis lung impairment: systematic review and meta-analysis of spirometry data from 14 621 people

Olena Ivanova[1,2,8], Verena Sophia Hoffmann[3,8], Christoph Lange[4,5,6,7], Michael Hoelscher[1,2] and Andrea Rachow[1,2]

Eur Respir Rev. 2023;32:220221.

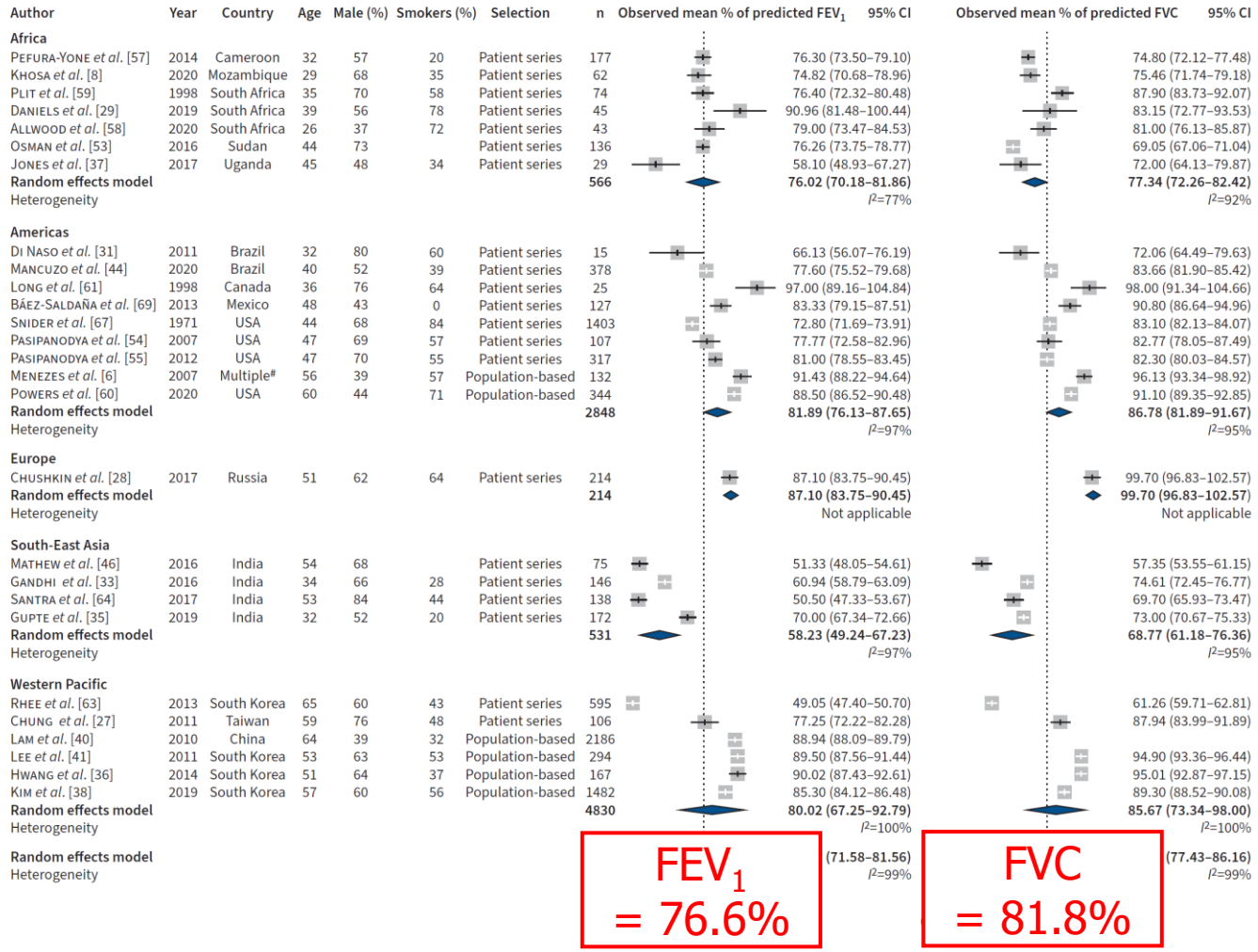
Post-TB lung impairment

- Meta-analysis
- 14,621 TB survivors (1971-2020)
- DS-TB and MDR-TB
- Time point for spirometry assessment
  : median 6M [IQR 0–26.5] after EOT



Post-TB lung impairment

DS-TB



Author	Year	Country	Age	Male (%)	Smokers (%)	Selection	n	Observed mean % of predicted FEV_1	95% CI	Observed mean % of predicted FVC	95% CI
Africa											
Pefura-Yone *et al.* [57]	2014	Cameroon	32	57	20	Patient series	177	76.30	(73.50–79.10)	74.80	(72.12–77.48)
Khosa *et al.* [8]	2020	Mozambique	29	68	35	Patient series	62	74.82	(70.68–78.96)	75.46	(71.74–79.18)
Plit *et al.* [59]	1998	South Africa	35	70	58	Patient series	74	76.40	(72.32–80.48)	87.90	(83.73–92.07)
Daniels *et al.* [29]	2019	South Africa	39	56	78	Patient series	45	90.96	(81.48–100.44)	83.15	(72.77–93.53)
Allwood *et al.* [58]	2020	South Africa	26	37	72	Patient series	43	79.00	(73.47–84.53)	81.00	(76.13–85.87)
Osman *et al.* [53]	2016	Sudan	44	73		Patient series	136	76.26	(73.75–78.77)	69.05	(67.06–71.04)
Jones *et al.* [37]	2017	Uganda	45	48	34	Patient series	29	58.10	(48.93–67.27)	72.00	(64.13–79.87)
Random effects model							**566**	**76.02**	**(70.18–81.86)**	**77.34**	**(72.26–82.42)**
Heterogeneity								I^2=77%		I^2=92%	
Americas											
Di Naso *et al.* [31]	2011	Brazil	32	80	60	Patient series	15	66.13	(56.07–76.19)	72.06	(64.49–79.63)
Mancuzo *et al.* [44]	2020	Brazil	40	52	39	Patient series	378	77.60	(75.52–79.68)	83.66	(81.90–85.42)
Long *et al.* [61]	1998	Canada	36	76	64	Patient series	25	97.00	(89.16–104.84)	98.00	(91.34–104.66)
Báez-Saldaña *et al.* [69]	2013	Mexico	48	43	0	Patient series	127	83.33	(79.15–87.51)	90.80	(86.64–94.96)
Snider *et al.* [67]	1971	USA	44	68	84	Patient series	1403	72.80	(71.69–73.91)	83.10	(82.13–84.07)
Pasipanodya *et al.* [54]	2007	USA	47	69	57	Patient series	107	77.77	(72.58–82.96)	82.77	(78.05–87.49)
Pasipanodya *et al.* [55]	2012	USA	47	70	55	Patient series	317	81.00	(78.55–83.45)	82.30	(80.03–84.57)
Menezes *et al.* [6]	2007	Multiple#	56	39	57	Population-based	132	91.43	(88.22–94.64)	96.13	(93.34–98.92)
Powers *et al.* [60]	2020	USA	60	44	71	Population-based	344	88.50	(86.52–90.48)	91.10	(89.35–92.85)
Random effects model							**2848**	**81.89**	**(76.13–87.65)**	**86.78**	**(81.89–91.67)**
Heterogeneity								I^2=97%		I^2=95%	
Europe											
Chushkin *et al.* [28]	2017	Russia	51	62	64	Patient series	214	87.10	(83.75–90.45)	99.70	(96.83–102.57)
Random effects model							**214**	**87.10**	**(83.75–90.45)**	**99.70**	**(96.83–102.57)**
Heterogeneity								Not applicable		Not applicable	
South-East Asia											
Mathew *et al.* [46]	2016	India	54	68		Patient series	75	51.33	(48.05–54.61)	57.35	(53.55–61.15)
Gandhi *et al.* [33]	2016	India	34	66	28	Patient series	146	60.94	(58.79–63.09)	74.61	(72.45–76.77)
Santra *et al.* [64]	2017	India	53	84	44	Patient series	138	50.50	(47.33–53.67)	69.70	(65.93–73.47)
Gupte *et al.* [35]	2019	India	32	52	20	Patient series	172	70.00	(67.34–72.66)	73.00	(70.67–75.33)
Random effects model							**531**	**58.23**	**(49.24–67.23)**	**68.77**	**(61.18–76.36)**
Heterogeneity								I^2=97%		I^2=95%	
Western Pacific											
Rhee *et al.* [63]	2013	South Korea	65	60	43	Patient series	595	49.05	(47.40–50.70)	61.26	(59.71–62.81)
Chung *et al.* [27]	2011	Taiwan	59	76	48	Patient series	106	77.25	(72.22–82.28)	87.94	(83.99–91.89)
Lam *et al.* [40]	2010	China	64	39	32	Population-based	2186	88.94	(88.09–89.79)		
Lee *et al.* [41]	2011	South Korea	53	63	53	Population-based	294	89.50	(87.56–91.44)	94.90	(93.36–96.44)
Hwang *et al.* [36]	2014	South Korea	51	64	37	Population-based	167	90.02	(87.43–92.61)	95.01	(92.87–97.15)
Kim *et al.* [38]	2019	South Korea	57	60	56	Population-based	1482	85.30	(84.12–86.48)	89.30	(88.52–90.08)
Random effects model							**4830**	**80.02**	**(67.25–92.79)**	**85.67**	**(73.34–98.00)**
Heterogeneity								I^2=100%		I^2=100%	
Random effects model									**(71.58–81.56)**		**(77.43–86.16)**
Heterogeneity									I^2=99%		I^2=99%

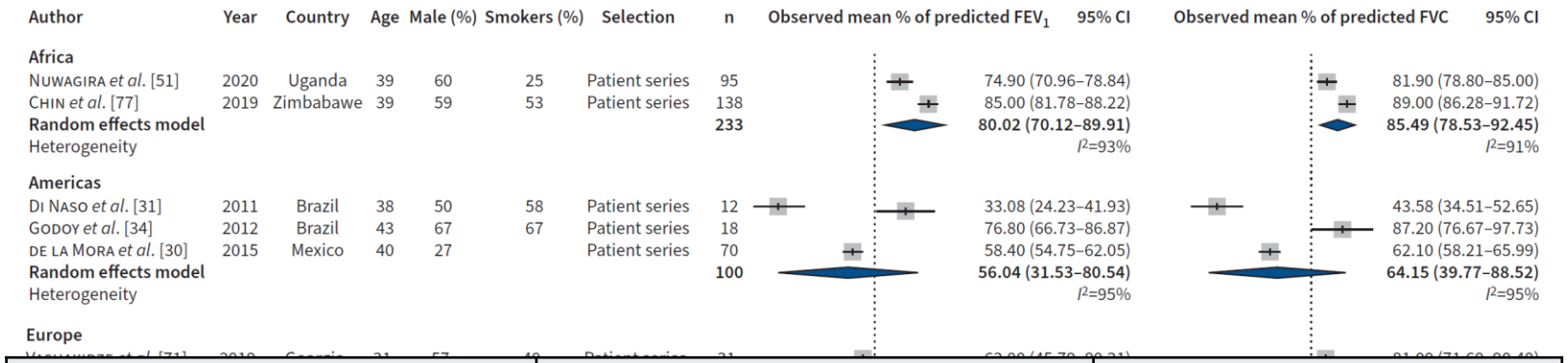
FEV_1 = 76.6%

FVC = 81.8%

Eur Respir Rev. 2023;32:220221.

Post-TB lung impairment

MDR-TB



(proportion)	DS-TB	MDR-TB
Obstructive	22%	19%
Restrictive	23%	22%
Mixed	15%	43%

Eur Respir Rev. 2023;32:220221.

REVIEW

Korean J Intern Med 2024;39:7-24
https://doi.org/10.3904/kjim.2023.395

Check for updates

KJIM

Long term management of people with post-tuberculosis lung disease

Wan Seo[1], Hyung Woo Kim[2], Ju Sang Kim[2], and Jinsoo Min[3]

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

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NEJM Evid. 2023;2:EVIDoa2300054.

High dose rifampin

- Current recommended dose of RIF : 10mg/kg/day
  - chosen in the 1960s, primarily because of cost
  - little data on maximum tolerated dose

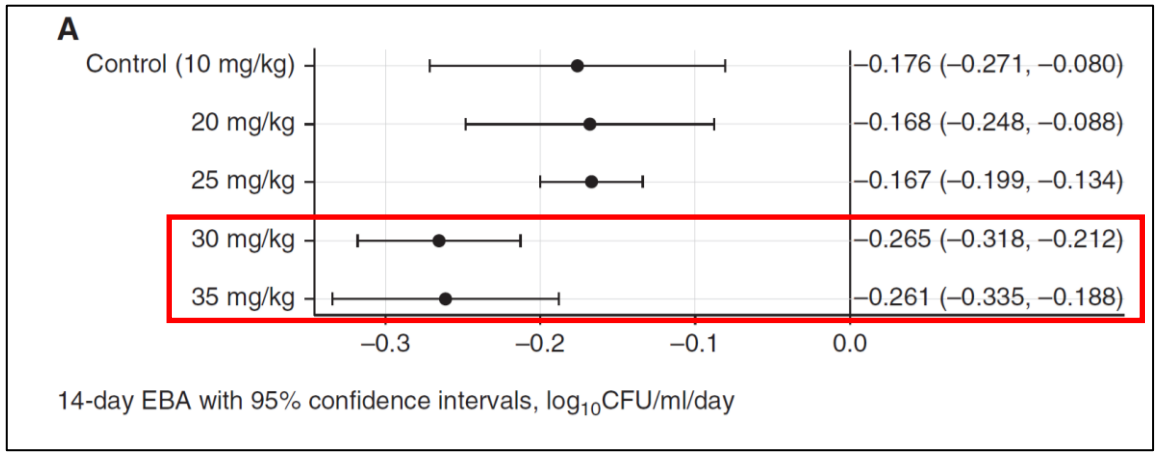


Table 2. Possibly Related and Definitely Related Adverse Events per Grade and per Dose Group

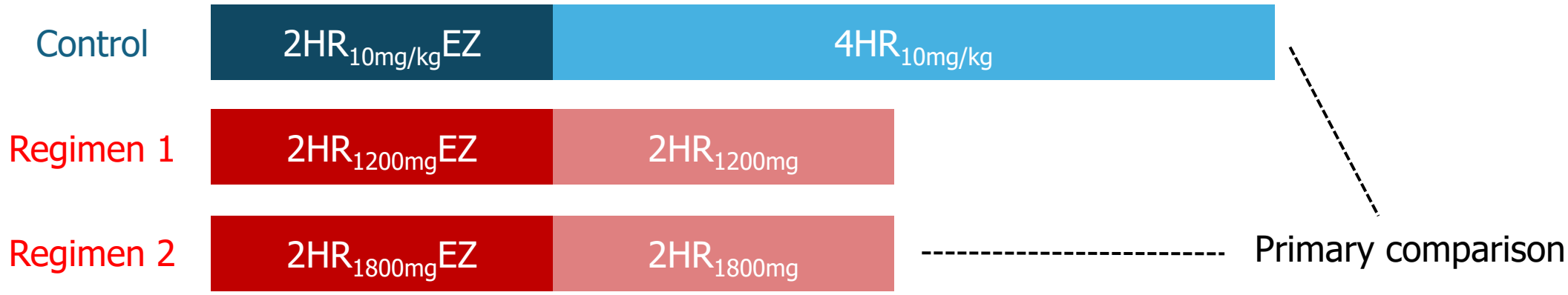
Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

Definition of abbreviation: RIF = rifampin.
*Among the grade 3 events, there was a case of transient hyperkalemia of 6.1 mmol/L in the 20 mg/kg RIF group that reoccurred in the same patient in Week 3 (counted as two events). Potassium values normalized with no specific measures and no ECG changes were recorded. In the 30 mg/kg RIF group, there was one grade 3 unrelated pleural effusion and a possibly related elevation of transaminase more than five times the upper limit of normal, which normalized spontaneously after repeat measurements. No grade 4 or grade 5 events were observed.

Am J Respir Crit Care Med. 2015;191:1058-65.

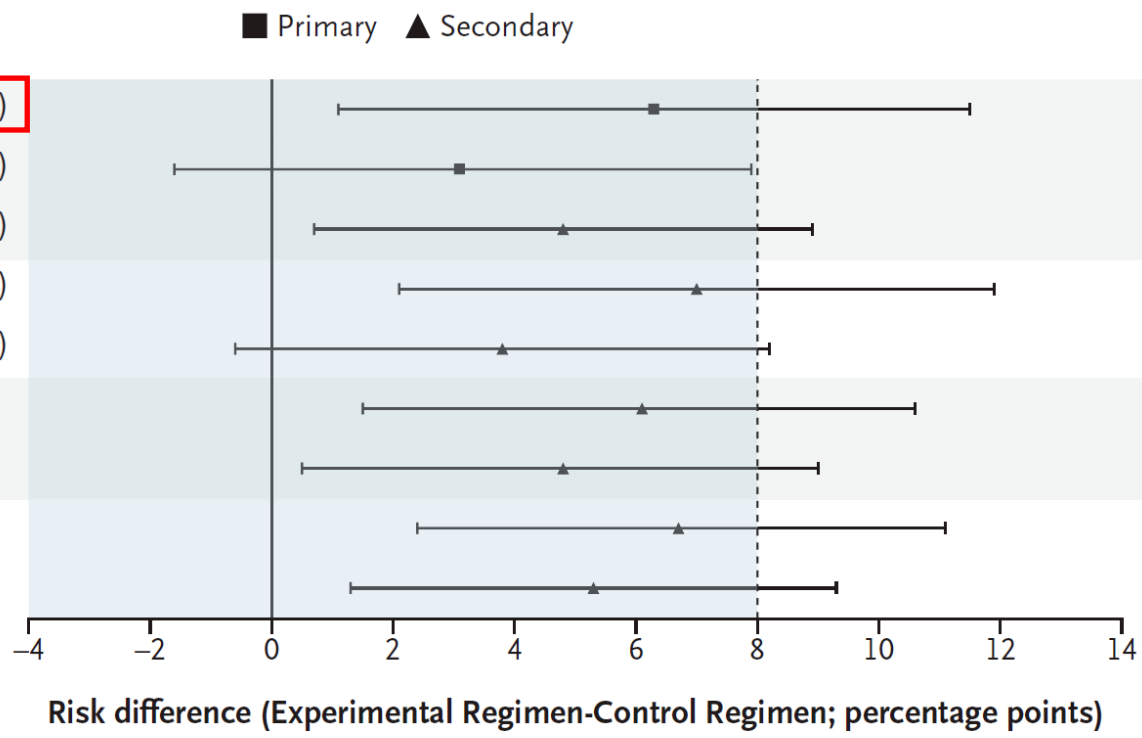
RIFASHORT trial

- Open-label, phase 3, randomized, non-inferiority trial
- Botswana, Uganda, Guinea, Nepal, Pakistan, Peru
- Rifampin-susceptible new pulmonary TB patients ≥ 18 yrs
- Primary end point: unfavorable outcome, 18M after enrollment



RIFASHORT trial

Study population	Study regimen	% Unfavorable	Control	aRD (90% CI)
mITT-M	SR2 (R 1800 mg)	13.4 (25/186)	7.0 (13/187)	6.3 (1.1 to 11.5)
	SR1 (R 1200 mg)	10.2 (19/186)	7.0 (13/187)	3.1 (–1.6 to 7.9)
	SR1 + SR2	11.8 (44/372)	7.0 (13/187)	4.8 (0.7 to 8.9)
mITT-All	SR2	13.4 (27/201)	6.3 (13/206)	7.0 (2.1 to 11.9)
	SR1	10.2 (21/206)	6.3 (13/206)	3.8 (–0.6 to 8.2)
PP-M	SR2	10.6 (19/180)	4.4 (8/182)	6.1 (1.5 to 10.6)
	SR1	9.3 (17/182)	4.4 (8/182)	4.8 (0.5 to 9.0)
PP-All	SR2	10.8 (21/195)	4.0 (8/201)	6.7 (2.4 to 11.1)
	SR1	9.4 (19/202)	4.0 (8/201)	5.3 (1.3 to 9.3)



NEJM Evid. 2023;2:EVIDoa2300054.

RIFASHORT trial

Table 2. Primary and Key Secondary Outcome Analyses.*

mITT-M Primary Analysis Assessable Outcomes	Control (n=187)	Study Regimen 1 (n=186)	Study Regimen 2 (n=186)
Favorable			
Participants with outcome — no. (%)	174 (93.0)	167 (89.8)	161 (86.6)
Unfavorable			
Participants with outcome — no. (%)	13 (7.0)	19 (10.2)	25 (13.4)
Adjusted percentage point difference from control (90% CI)		3.1 (–1.6 to 7.9)	6.3 (1.1 to 11.5)
Reasons for unfavorable outcome			
Death during the treatment phase	3 (1.6)	4 (2.2)	0
Posttreatment death, TB a plausible cause	0	1 (0.5)	0
Lost to follow-up during the treatment phase	2 (1.1)	0	1 (0.5)
Withdrew from the trial during the treatment phase†	3 (1.6)	2 (1.1)	5 (2.7)
Change in treatment because of adverse event‡	1 (0.5)	2 (1.1)	7 (3.8)
Two consecutive positive cultures after completing treatment	2 (1.1)	9 (4.8)	9 (4.8)
Retreated for TB because of clinical signs and symptoms without 2 consecutive positive cultures	2 (1.1)	1 (0.5)	3 (1.6)
Unassessable outcomes	4	6	9
Posttreatment death deemed unrelated to TB or treatment	2	1	2
Posttreatment LTFU when culture negative	1	3	5
Evidence of exogenous TB reinfection	0	1	2
Withdrawal during the treatment phase when culture negative	1	0	0
Posttreatment withdrawal when culture negative	0	1	0
Secondary analysis outcomes			
Confirmed culture conversion from positive to negative — n/N (%)			
8 weeks from randomization	158/184 (85.9)	166/179 (92.7)	164/182 (90.1)
12 weeks from randomization	182/185 (98.4)	180/184 (97.8)	184/187 (98.4)

NEJM Evid. 2023;2:EVIDoa2300054.

RIFASHORT trial

Table 3. Laboratory-Defined and Clinical Adverse Events According to Treatment Group.*

Participants Experiencing	Control (n=224)	Study Regimen 1 (n=223)	Study Regimen 2 (n=225)
Primary safety outcome			
Grade 3 or 4 adverse event — no. (%)	9 (4.0)	10 (4.5)	10 (4.4)
Percentage point difference from control (95% CI)		0.5 (–3.3 to 4.2)	0.4 (–3.3 to 4.2)
Secondary safety outcome			
Grade 1–4 adverse event — no. (%)	120 (53.6)	109 (48.9)	115 (51.1)
Percentage point difference from control (95% CI)		–4.7 (–13.9 to 4.6)	–2.5 (–11.7 to 6.8)
Other safety outcomes — no. (%)			
Serious adverse event	3 (1.3)	3 (1.3)	3 (1.3)
Notifiable adverse event	10 (4.5)	13 (5.8)	13 (5.8)
Notifiable adverse event, excluding pregnancy	6 (2.7)	11 (4.9)	13 (5.8)
Death	5 (2.2)	8 (3.6)	3 (1.3)
Hepatotoxicity outcomes			
ALT>180 U/l (5×ULN, grade 3) — no. (%)	3 (1.3)	7 (3.1)	7 (3.1)
ALT>360 U/l (10×ULN, grade 4) — no. (%)	2 (0.9)	1 (0.4)	4 (1.8)
Grade 3/4 ALT results, U/l — median (IQR; max)	387 (237–511; 511)	212 (189–350; 449)	377 (332–450; 942)
Total bilirubin >3 mg/dl (2.6×ULN, grade 3) — no. (%)	1 (0.4)	1 (0.4)	6 (2.7)
Total bilirubin >6 mg/dl (5×ULN, grade 4) — no. (%)	1 (0.4)	0	3 (1.3)
Grade 3/4 total bilirubin results, mg/dl — median (IQR; max)	12.1	3.2	5.4 (4.1–9.4; 29.5)
Satisfies Hy's law (ALT>3×ULN and total bilirubin >2×ULN) — no. (%)	0	1 (0.4)	2† (0.9)

NEJM Evid. 2023;2:EVIDoa2300054.

The Xpert MTB/RIF Cycle Threshold Value Predicts *Mycobacterium tuberculosis* Transmission to Close Contacts in a Brazilian Prospective Multicenter Cohort

Leandro S. Garcia,[1,2,a] Allyson G. Costa,[1,2,3,4,a] Mariana Araújo-Pereira,[5,6,7,a] Renata Spener-Gomes,[1,2] Amanda França Aguiar,[1] Alexandra B. Souza,[1,2] Lucas O. A. Lima,[1,8] Aline Benjamin,[9] Michael S. Rocha,[7,10] Adriana S. R. Moreira,[11] Jaquelane Silva,[1] Saulo R. N. Santos,[10] Maria Cristina Lourenço,[9] Marina C. Figueiredo,[12] Megan M. Turner,[12] Afranio L. Kritski,[11] Valeria C. Rolla,[9] Timothy R. Sterling,[12] Bruno B. Andrade,[5,6,7,b] and Marcelo Cordeiro-Santos[1,2,b]; RePORT Brazil Consortium

Clin Infect Dis. 2024:ciad794.

Xpert Ct value and TB transmission

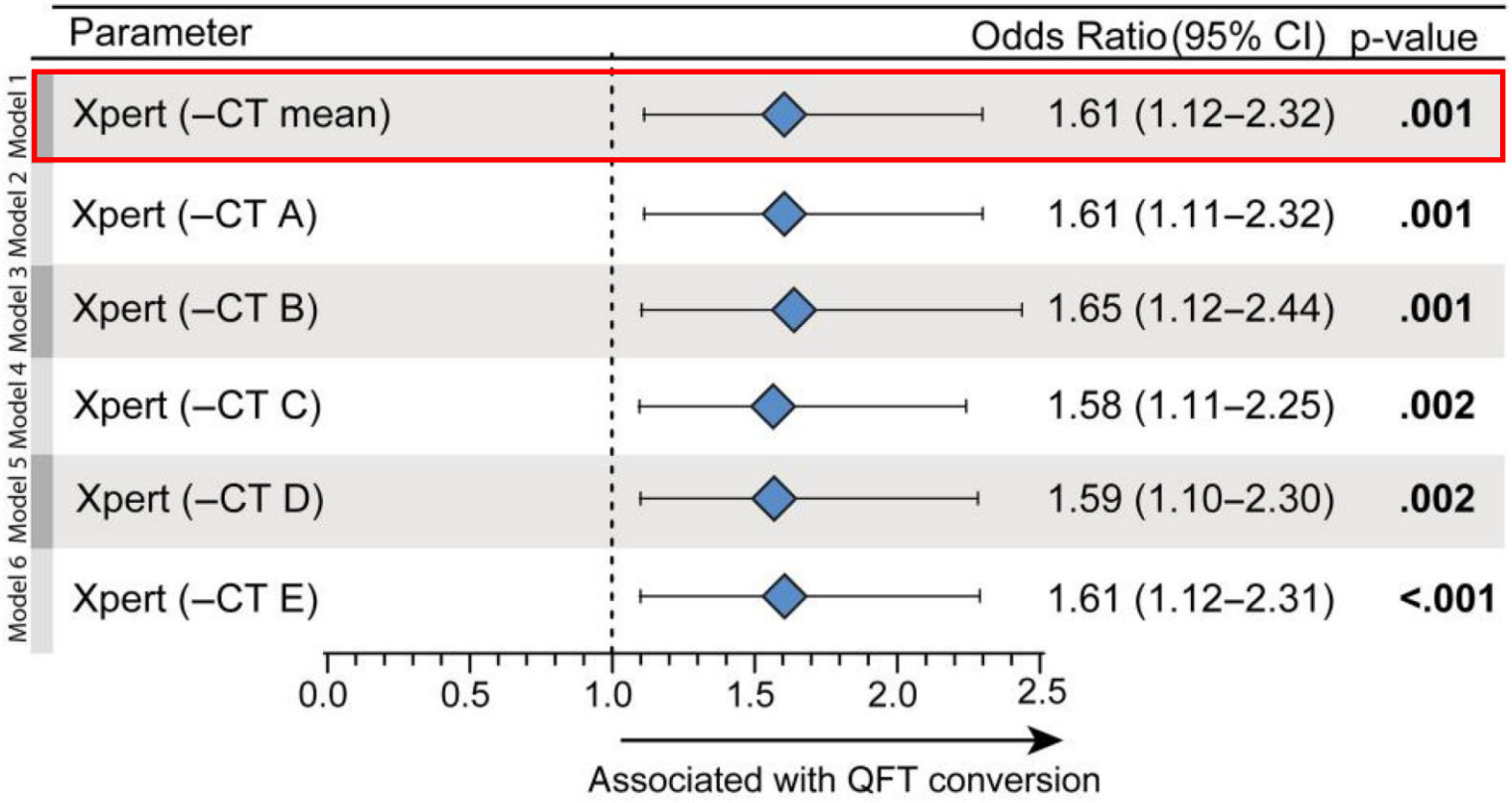
Xpert MTB/RIF cycle threshold (Ct) values
↔ AFB smear, time to positivity in culture
↔ Bacillary load

- Prospective study, Brazil
- Culture-confirmed PTB patients and their close contact
- Xpert MTB/RIF Ct values (index case)

  → QTFplus results (close contact*) [baseline, 6M and conversion]

*≥4 hours of exposure per week with the TB index case at any time in the 6 months prior to TB diagnosis

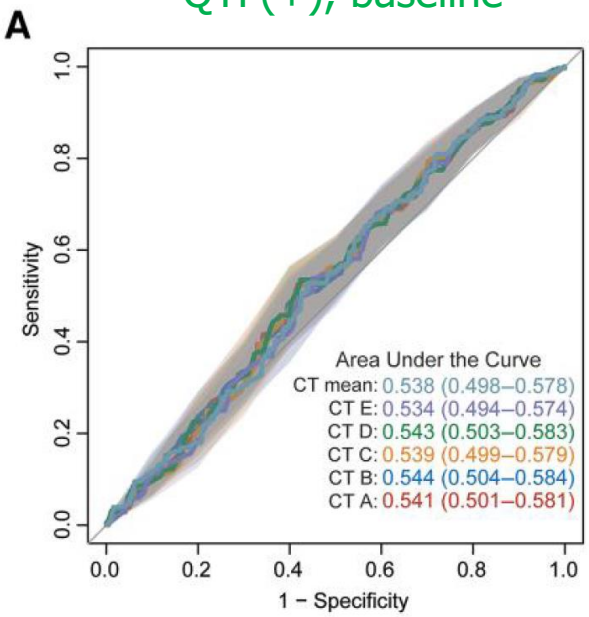
Xpert Ct value and TB transmission



Clin Infect Dis. 2024:ciad794.

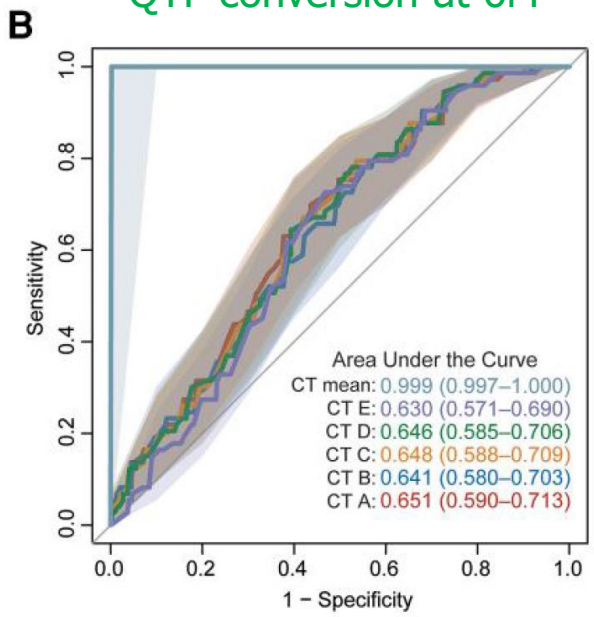
Xpert Ct value and TB transmission

QTF(+), baseline



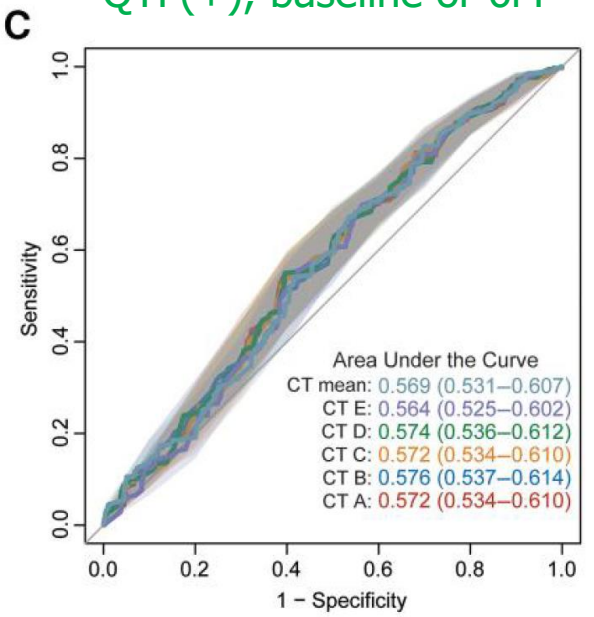
	Threshold	Specificity	Sensitivity
CT A	18.4	0.58 (0.55–0.63)	0.53 (0.47–0.58)
CT B	19.5	0.6 (0.56–0.64)	0.49 (0.43–0.54)
CT C	18.6	0.58 (0.54–0.62)	0.52 (0.47–0.58)
CT D	19.6	0.58 (0.54–0.61)	0.54 (0.48–0.60)
CT E	22.1	0.41 (0.37–0.45)	0.68 (0.63–0.73)
CT mean	19.3	0.56 (0.52–0.60)	0.53 (0.47–0.60)

QTF conversion at 6M



	Threshold	Specificity	Sensitivity
CT A	18.7	0.56 (0.52–0.61)	0.70 (0.59–0.79)
CT B	21.7	0.40 (0.45–0.49)	0.78 (0.68–0.86)
CT C	20.3	0.46 (0.42–0.51)	0.79 (0.70–0.88)
CT D	20.9	0.49 (0.44–0.53)	0.77 (0.67–0.86)
CT E	20.5	0.54 (0.49–0.58)	0.73 (0.63–0.82)
CT mean	20.8	0.47 (0.42–0.51)	0.78 (0.68–0.88)

QTF(+), baseline or 6M



	Threshold	Specificity	Sensitivity
CT A	18.4	0.61 (0.57–0.65)	0.54 (0.48–0.59)
CT B	21.7	0.45 (0.40–0.30)	0.68 (0.63–0.73)
CT C	18.6	0.60 (0.56–0.65)	0.53 (0.48–0.59)
CT D	19.5	0.60 (0.56–0.65)	0.55 (0.49–0.60)
CT E	22.1	0.41 (0.37–0.45)	0.71 (0.66–0.76)
CT mean	20.9	0.46 (0.42–0.51)	0.67 (0.62–0.72)

Clin Infect Dis. 2024:ciad794.

A Systematic Review and Meta-Analysis of Tuberculous Preventative Therapy Adverse Events

Luca Melnychuk,[1] Sara Perlman-Arrow,[2] Mayara Lisboa Bastos,[1,3,4] and Dick Menzies[1,2,3,4]

Clin Infect Dis. 2023;77:287-94.

Recommended TPT regimens

	6H	9H	3HR	3HP	4R
WHO	O	O	O	O	Δ
NHS	O		O (3-4M)		
CDC	Δ	Δ	O	O	O

권고요약

· 잠복결핵감염 치료를 결정하기 전에 반드시 활동성 결핵의 가능성을 배제하여야 한다.

· 잠복결핵감염 표준치료는 리팜핀을 포함한 단기요법인 리팜핀 4개월 요법(4R, IA), 3개월 이소니아지드/리팜핀 요법(3HR, IIA)을 권고하나, 이소니아지드 9개월 요법(9H, IB)도 선택적으로 고려할 수 있다.

· 최근 전염성 결핵 환자의 접촉자인 경우 약제 선택 시 전염원(index case)의 약제감수성 검사 결과를 참고한다.

· 잠복결핵감염 치료 전 기저 혈액검사를 시행하고 간독성 위험군에서는 규칙적으로 혈액검사를 시행한다(IIA).

· 잠복결핵감염 치료 중 활동성 결핵이 발생하면 치료에 사용중인 약제를 포함하여 초치료 표준처방으로 치료를 시작한다(IIIA).

TPT adverse event

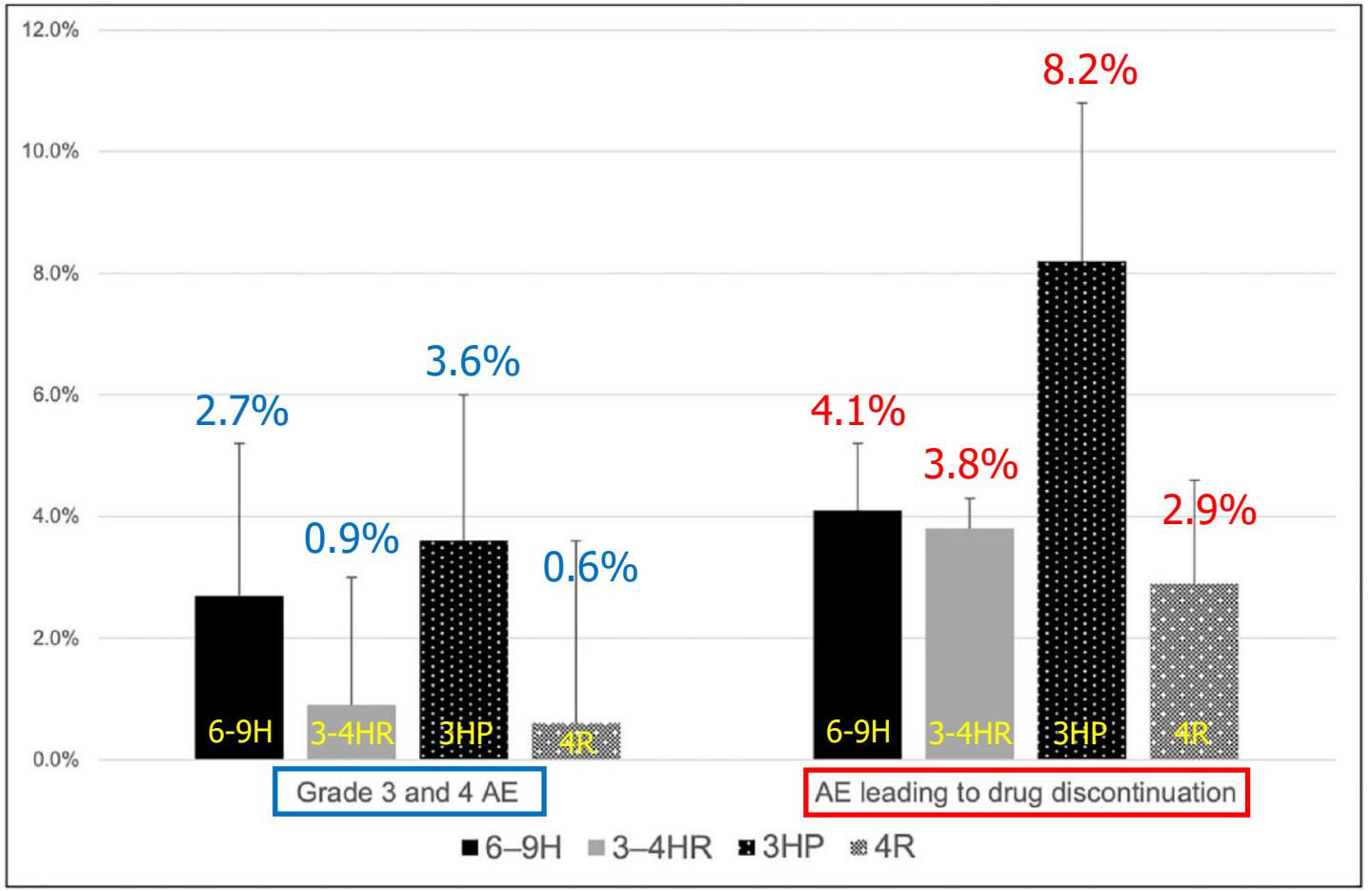
- Meta-analysis
- 186,281 participants (1952–2021)
- Any AE, AE leading to drug discontinuation

  Hepato-toxic AE, drug discontinuation due to hepato-toxic AE

- 6-9H vs. 3-4HR vs. 3HP vs. 4R

TPT adverse event

Any AE



Clin Infect Dis. 2023;77:287-94.

TPT adverse event

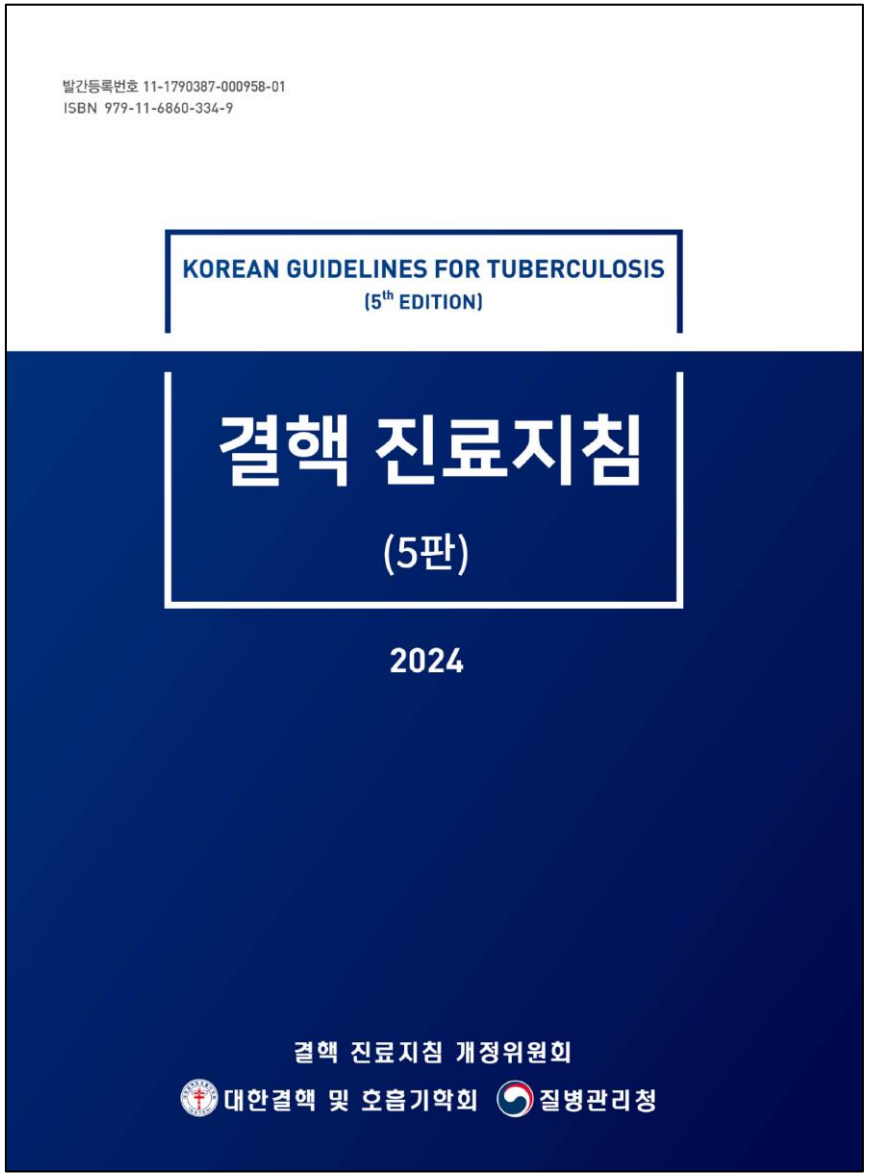
Hepatotoxicity

Table 4. Pooled Estimates of Cumulative Incidence of Hepatotoxicity by Regimen (All Ages)

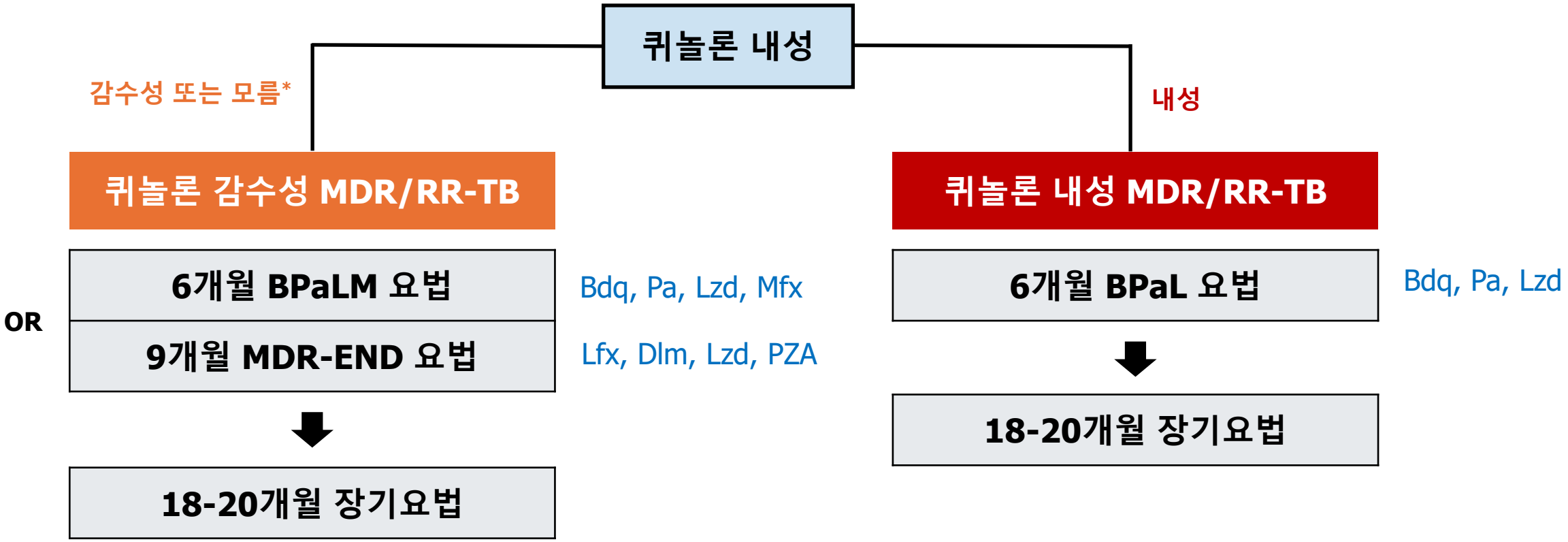
Regimen	Outcome	Hepatoxicity Judged to Be Related to Study Drug[a]	Grade 3 and 4 Hepatotoxicity[b,c]	Hepatoxicity Leading to Study Drug Discontinuation[b]	Death Due to Hepatoxicity Judged to Be Related to the Study Drug[b]
≥24H	N cohort	2	6	4	7
	n/N	184/1303	66/2482	19/2021	2/2482
	Estimate (95% CI)	5.9% (1% to 27.7%) ‡‡‡	2.6% (1.3% to 5.3%) ‡	0.9% (0% to 10.8%) ‡	0.081% (0% to .249%)
12H	N cohort	7	5	9	11
	n/N	129/8815	58/1695	73/9658	3/8967
	Estimate (95% CI)	0.9% (.2% to 3.8%) ‡‡‡	3.1% (.9% to 9.6%) ‡‡‡	0.8% (.3% to 2.2%) ‡‡‡	0.033% (.005% to .087%)
6–9H	N cohort	75	2.1%	2.2%	95
	n/N	1193/36 775			4/64 359
	Estimate (95% CI)	3.3% (2.3% to 4.8%) ‡‡‡	2.1% (1.5% to 3.1%) ‡‡‡	2.2% (1.6% to 3.0%) ‡‡‡	0.0001% (0% to .01297%)
3–4HR	N cohort	9	1.4%	1.5%	21
	n/N	96/1153			0/3092
	Estimate (95% CI)	5.2% (2% to 12.9%) ‡‡‡	1.4% (0.7% to 2.7%) ‡	1.5% (.9% to 2.6%) ‡	0% (0%,0%)
3HP	N cohort	17	1.0%	0.8%	27
	n/N	130/8881			0/12 119
	Estimate (95% CI)	1.6% (.9% to 3%)‡‡‡	1.0% (.7% to 1.2%) ‡	0.8% (.5% to 1.4%) ‡	0% (0%, 0%)
4R	N cohort	18	0.4%	0.2%	22
	n/N	63/6535			0/5427
	Estimate (95% CI)	0.6% (.2% to 2.0%) ‡‡‡	0.4% (.2% to .8%) ‡	0.2% (.1% to .6%) ‡	0% (0%, 0%)
Placebo	N cohort	3	4	6	6
	n/N	25/684	46/1599	13/2119	0/1769
	Estimate (95% CI)	0.1% (.0% to 43.5%) ‡	2.5% (1.1% to 6%) ‡‡‡	0% (0% to 47.4%) ‡	0% (0%, 0%)
Controls—no treatment	N cohort	Not applicable	5	Not applicable	Not applicable
	n/N	Not applicable	9/3937	Not applicable	Not applicable
	Estimate (95% CI)	Not applicable	0.2% (.1% to .4%) ‡‡	Not applicable	Not applicable

Clin Infect Dis. 2023;77:287-94.

Shorter MDR/RR-TB Treatment Regimen in 2024 Korean guideline



MDR/RR-TB Tx (2024 국내 개정지침)



* 다음의 경우는 제외 (퀴놀론 내성 다제내성결핵에 준하여 치료 시작)
- 퀴놀론 내성 다제내성결핵의 과거력
- 퀴놀론 내성 다제내성결핵 환자의 밀접접촉자에서 발생한 결핵

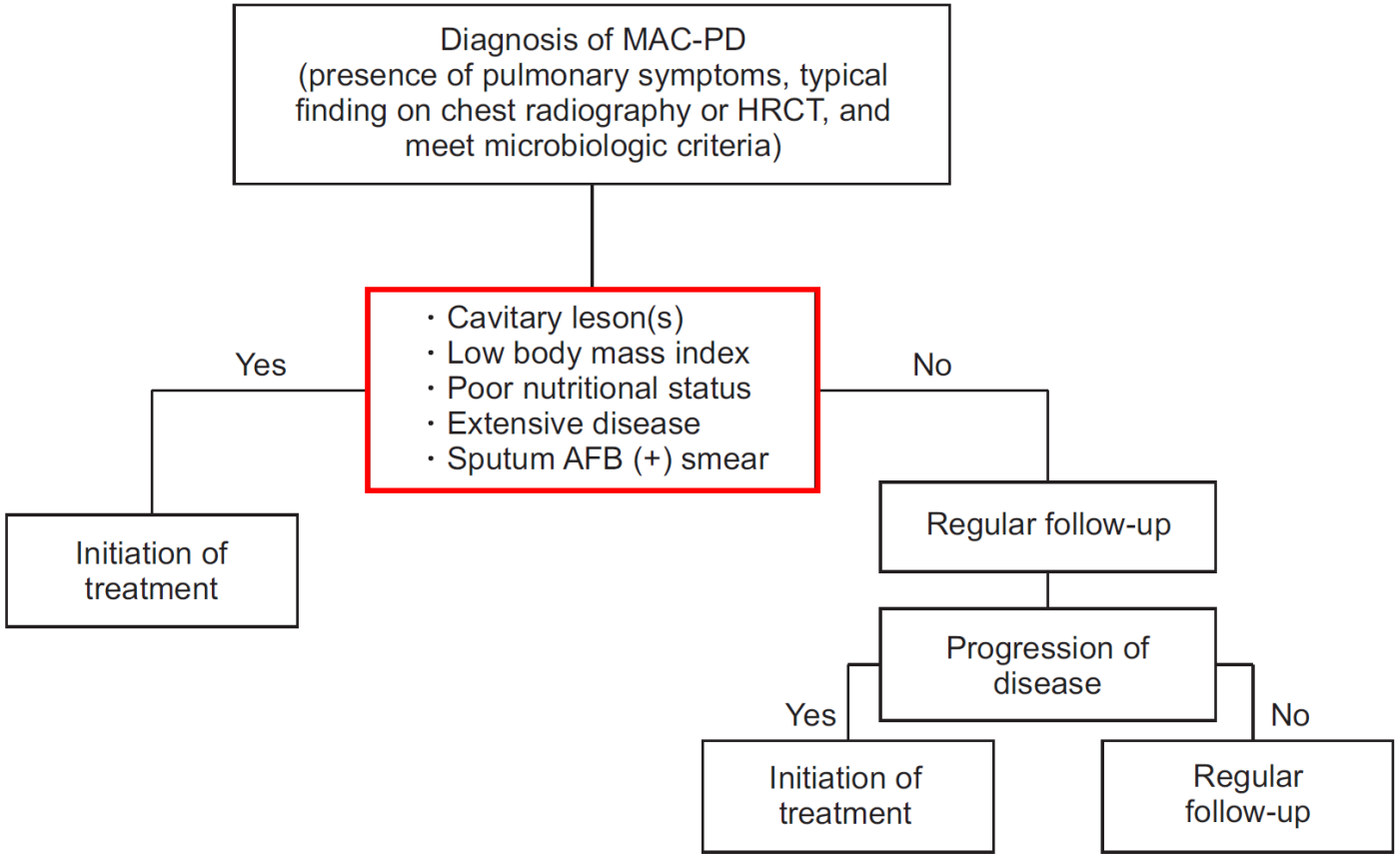
NTM

Spontaneous Cultural Conversion Rate of *Mycobacterium avium* Complex Pulmonary Disease Based on BACES Severity

Bo-Guen Kim [1,†], Jin Young Yu [2,†] and Byung Woo Jhun [3,*]

J Clin Med. 2023;12:7125.

Treatment decision of NTM-PD



Tuberc Respir Dis (Seoul). 2019;82:15-26.

BACES score for mortality prediction

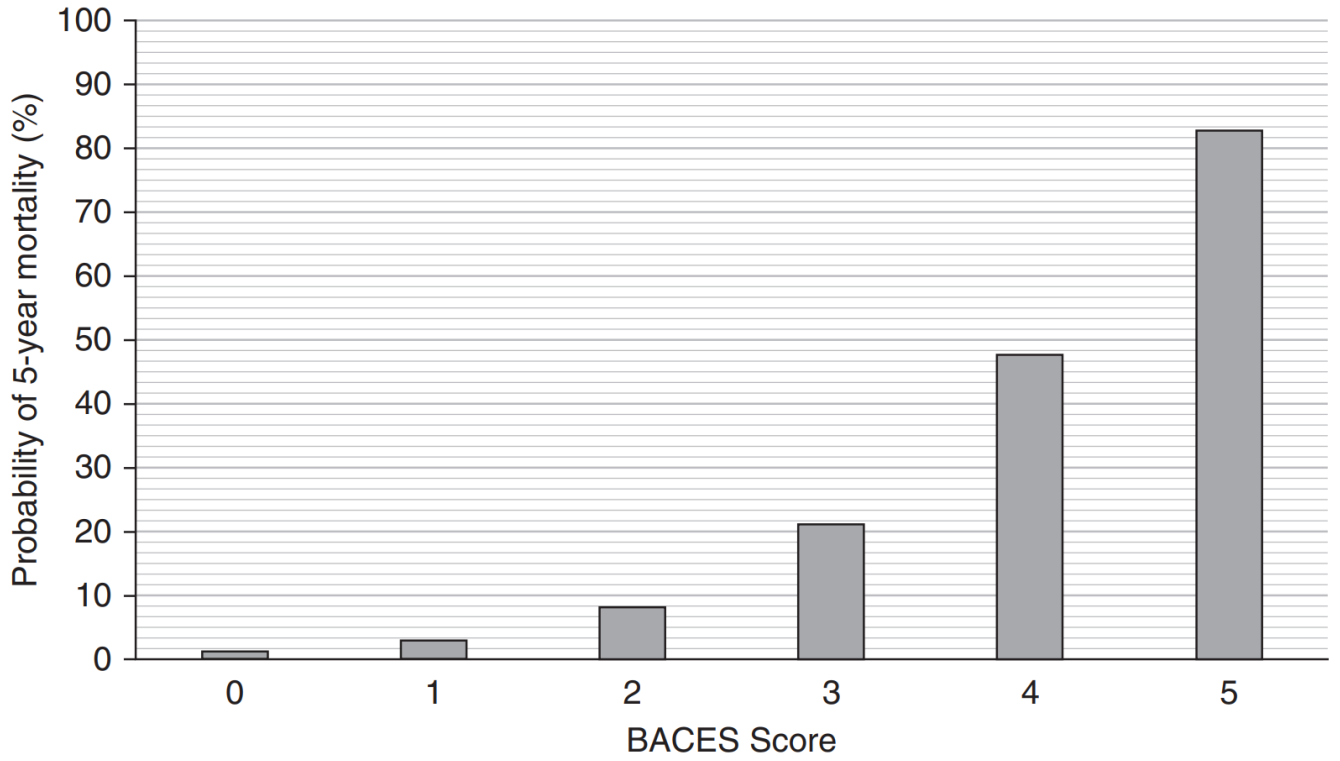
BMI < 18.5 kg/m^2 (1 point)

Age ≥ 65 years (1 point)

Cavity + (1 point)

ESR elevation (1 point)
(Men >15mm/h, Women >20mm/h)

Male **S**ex (1 point)



Am J Respir Crit Care Med. 2021;203:230-6.

BACES score and SCC

- Retrospective study, Samsung Medical Center (2002-2016)
- MAC-PD patients with watchful waiting (no antibiotics)
- Baseline BACES score ↔ SCC and favorable outcome
  - SCC : at least 3 consecutive negative culture results (4wks interval)
  - favorable outcome: maintaining SCC or having two consecutive negative sputum cultures until the last follow-up date

- BACES score category: mild (0–1 point), moderate (2–3 points), severe (4–5 points)
- Median follow-up duration: 48M (IQR 26.4–76.4)

BACES score and SCC

Watchful Waiting	Total (n = 373)	Mild (n = 183)	Moderate (n = 157)	Severe (n = 33)	p-Value	p-Trend †
Spontaneous negative culture conversion	153 (41)	87/183 (48)	58/157 (37)	8/33 (24)	0.017 [ac]	0.005
Time to culture conversion, months	6.2 (2.7–17.7)	6.0 (2.2–16.1)	5.4 (2.8–17.2)	22.1 (14.2–88.5)	0.008 [bc]	0.037
Favorable outcome *	157 (42)	97/183 (53)	54/157 (34)	6/33 (18)	<0.001 [ac]	<0.001
Time to favorable outcome, months	6.2 (2.5–15.8)	6.2 (2.3–14.3)	5.4 (2.5–14.0)	40.3 (11.8–98.2)	0.022 [bc]	0.346

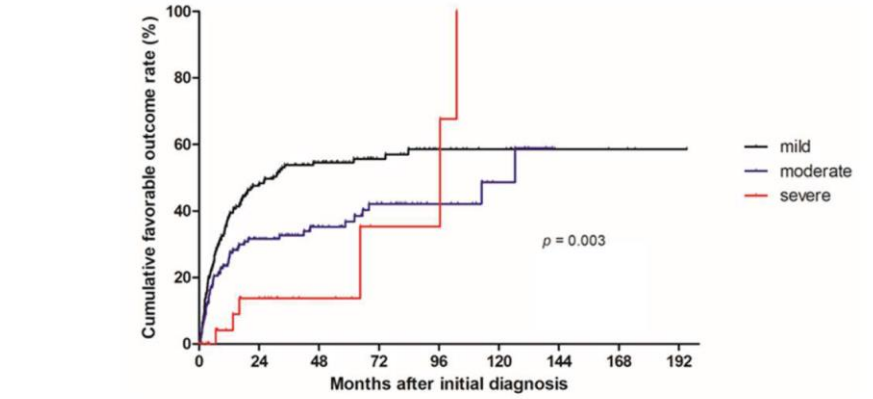


Figure 2. Cumulative favorable outcome rate in all study patients according to BACES severity.

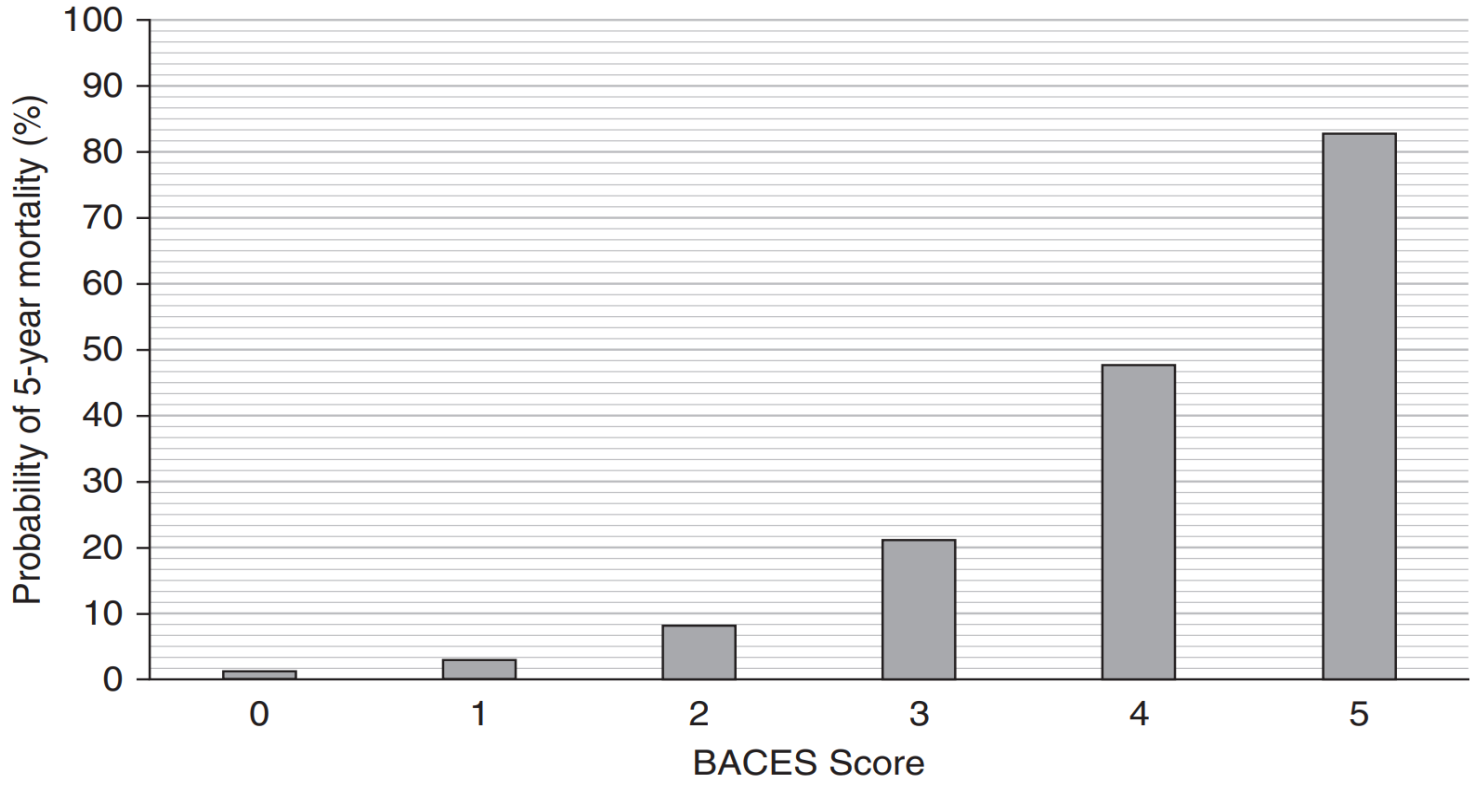
J Clin Med. 2023;12:7125.

BACES score and SCC

Variables	Univariable Analysis		Multivariable Analysis	
	Unadjusted HR (95% CI)	*p*-Value	Adjusted HR (95% CI)	*p*-Value
	Spontaneous negative culture conversion			
Ex- or current smoker	0.85 (0.59–1.22)	0.388	0.99 (0.66–1.49)	0.971
Underlying condition				
Previous pulmonary tuberculosis	1.02 (0.72–1.46)	0.901	1.12 (0.77–1.62)	0.556
Chronic obstructive pulmonary disease	1.54 (0.91–2.58)	0.106	1.76 (1.02–3.05)	0.043
Lung cancer	0.92 (0.40–2.07)	0.915	0.89 (0.38–2.08)	0.792
Etiology				
M. avium	Reference		Reference	
M. intracellulare	0.83 (0.60–1.17)	0.287	0.83 (0.59–1.17)	0.295
BACES severity				
Mild	Reference		Reference	
Moderate	0.75 (0.54–1.05)	0.093	0.74 (0.52–1.07)	0.106
Severe	0.53 (0.26–1.10)	0.089	0.49 (0.22–1.08)	0.076
Positive sputum AFB smear at diagnosis	0.68 (0.47–0.97)	0.034	0.70 (0.48–1.01)	0.057
	Favorable outcome *			
Ex- or current smoker	0.77 (0.53–1.12)	0.167	1.04 (0.69–1.57)	0.861
Underlying condition				
Previous pulmonary tuberculosis	0.83 (0.58–1.19)	0.313	0.95 (0.65–1.38)	0.767
Chronic obstructive pulmonary disease	1.11 (0.63–1.95)	0.728	1.35 (0.75–2.44)	0.317
Lung cancer	0.89 (0.40–2.02)	0.785	1.01 (0.44–2.33)	0.982
Etiology				
M. avium	Reference		Reference	
M. intracellulare	0.67 (0.48–0.94)	0.021	0.67 (0.47–0.94)	0.020
BACES severity				
Mild	Reference		Reference	
Moderate	0.63 (0.45–0.88)	0.007	0.63 (0.44–0.91)	0.013
Severe	0.37 (0.16–0.84)	0.017	0.37 (0.16–0.90)	0.028
Positive sputum AFB smear	0.79 (0.55–1.12)	0.787	0.84 (0.59–1.20)	0.333

J Clin Med. 2023;12:7125.

BACES score for Tx decision



Watchful waiting

Consider treatment
Frequent follow-up

Comparison of treatment outcomes between intermittent and daily regimens in non-cavitary nodular bronchiectatic-type *Mycobacterium avium* complex pulmonary disease in relation to sputum smear results: a retrospective cohort study

Junghee Jung,[1] Yong Pil Chong,[2] Hyun Joo Lee,[3] Tae Sun Shim,[4] Kyung-Wook Jo[4]

Antimicrob Agents Chemother. 2023;67:e0100323.

MAC-PD treatment

ATS/ERS/ESCMID/IDSA guideline (2020)

Organism	Number of drugs	Preferred drug regimen[#]	Dosing frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	⩾3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[¶]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[+]	⩾4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[¶]	Daily (3 times weekly may be used with aminoglycosides)

Eur Respir J. 2020;56:2000535.

MAC-PD treatment

BTS guideline (2017)

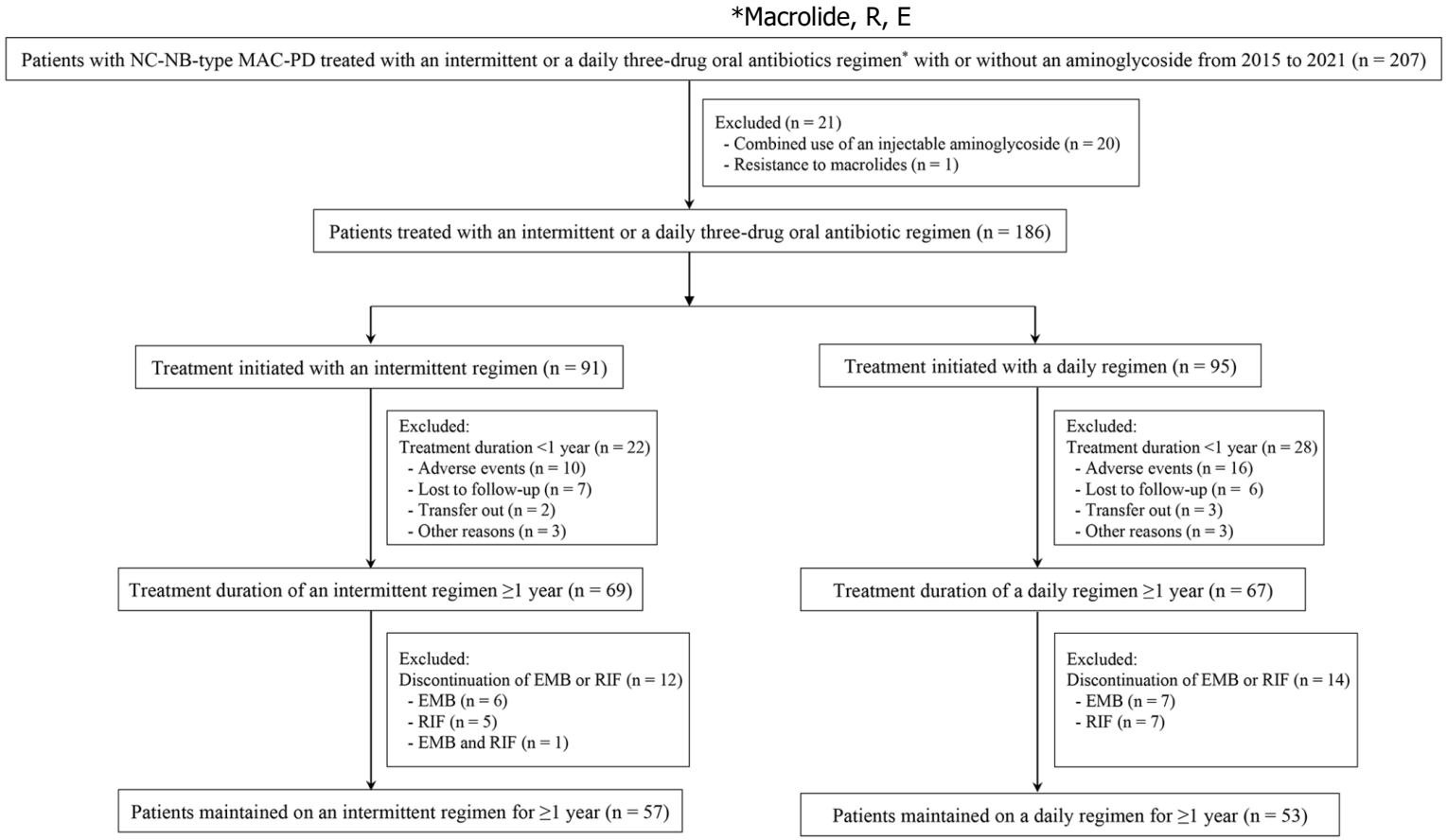
Table 3 Suggested antibiotic regimens for adults with *Mycobacterium avium* complex (MAC)-pulmonary disease

MAC-pulmonary disease	Antibiotic regimen
TIW **Non-severe MAC-pulmonary disease** (ie, AFB smear negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-to-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg 3×per week and Ethambutol 25 mg/kg 3×per week and Azithromycin 500 mg 3×per week or Clarithromycin 1 g in two divided doses 3 x per week. Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Daily **Severe MAC-pulmonary disease** (ie, AFB smear positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Clarithromycin-resistant MAC-pulmonary disease	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Isoniazid 300 mg (+pyridoxine 10 mg) daily or moxifloxacin 400 mg daily and Consider intravenous amikacin for up to 3 months or nebulised amikacin. Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

Thorax. 2017;72(Suppl 2):ii1-ii64.

Daily Tx for smear (+) NC-NB MAC-PD

- Retrospective study
- Asan Medical Center (2015-2021)



Antimicrob Agents Chemother. 2023;67:e0100323.

Daily Tx for smear (+) NC-NB MAC-PD

TABLE 1 Clinical characteristics and treatment outcome of patients with non-cavitary nodular bronchiectatic-type *Mycobacterium avium* complex pulmonary disease stratified by the treatment regimen[a,c]

		Culture conversion rate	P-value
AFB smear (+) (n=36)	Intermittent regimen	50.0%	0.034
	Daily regimen	85.0%	
AFB smear (-) (n=74)	Intermittent regimen	78.0%	0.098
	Daily regimen	93.9%	

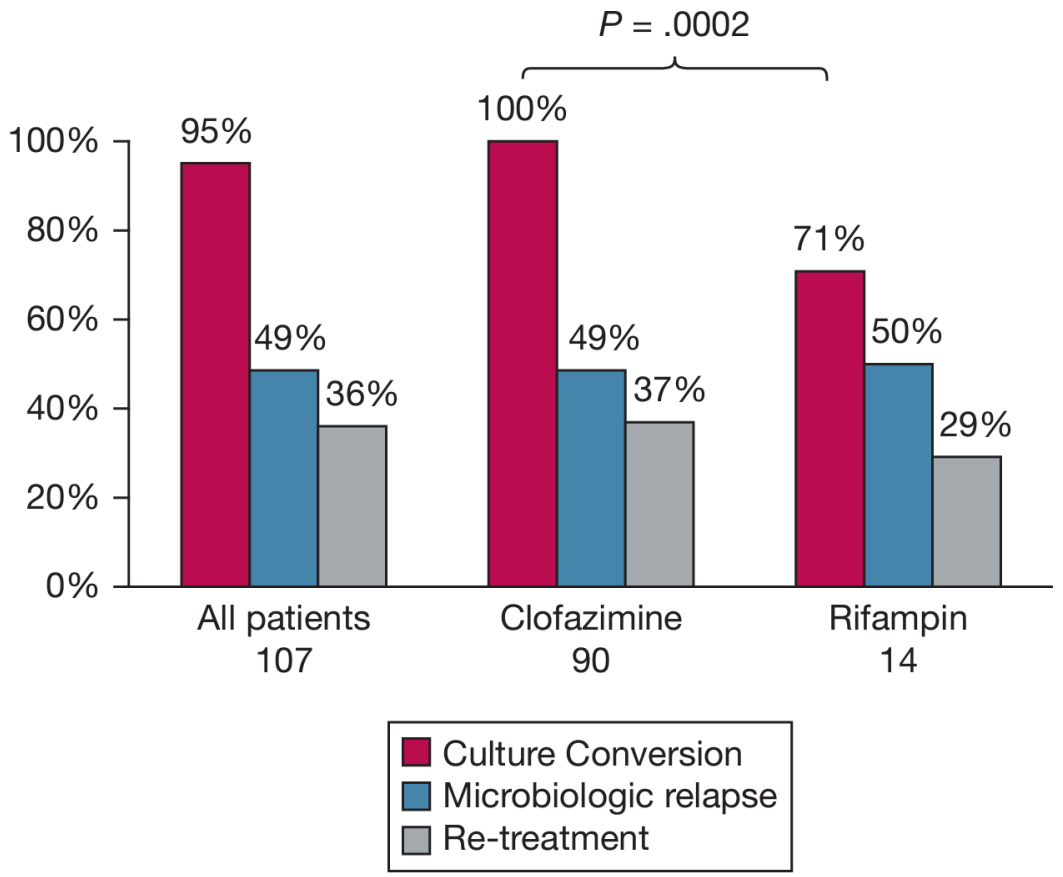
Antimicrob Agents Chemother. 2023;67:e0100323.

Treatment Outcomes of Clofazimine-Containing Regimens in Severe *Mycobacterium avium* Complex Pulmonary Disease

Inhan Lee,[1] Eui Jin Hwang,[2] Joong-Yub Kim,[1] Jae-Joon Yim,[1] and Nakwon Kwak[1,]

Open Forum Infect Dis. 2023;11:ofad682.

Clofazimine for MAC-PD treatment



Chest. 2016;149:1285-93.

Clofazimine for MAC-PD treatment

- Retrospective study, Seoul National University Hospital (2011-2022)
- Severe MAC-PD (smear +, cavity, severe symptoms/systemic illness, extensive disease)
- Clofazimine-containing regimen within the first 3M of treatment initiation (instead of amikacin)
- Culture conversion within 6M, microbiological cure

Drug used : macrolide (99%), ethambutol (88%), rifampin (9%)

Clofazimine dose (in general, SNUH)

- 50mg/day (BW ≤ 50kg)
- 100mg/day (BW > 50kg)

Clofazimine for MAC-PD treatment

Table 2. Treatment Outcomes and Adverse Events

Outcome	Total (N = 170)	Maintenance Dose		*P* Value[a]
		50 mg (n = 68)	100 mg (n = 102)	
Total treatment duration, median (IQR)	18.6 (12.4–25.8)	17.1 (10.9–22.4)	19.7 (12.6–29.4)	.015
Clofazimine use duration, median (IQR)	13.3 (8.6–20.6)	12.8 (8.7–18.2)	13.8 (8.5–22.1)	.130
Culture conversion within 6 mo	77 (45.3)	34 (50.0)	43 (42.2)	.348
Microbiological cure[b]	84/154 (54.6)	33/61 (54.1)	51/93 (54.8)	>.999
Adverse drug reactions necessitating the discontinuation of clofazimine	25 (14.7)	9 (13.2)	16 (15.7)	.658
Skin pigmentation	9 (5.3)	3 (4.4)	6 (5.9)	.743
Hepatotoxicity	8 (4.7)	3 (4.4)	5 (4.9)	>.999
Gastrointestinal discomfort	6 (3.5)	3 (4.4)	3 (2.9)	.684
QTc prolongation	2 (1.2)	0 (0.0)	2 (2.0)	.517

Open Forum Infect Dis. 2023;11:ofad682.

Clofazimine for MAC-PD treatment

Table 3. Predictive Factors for Culture Conversion Within 6 Months and Microbiological Cure (Multivariate)

Factor	Culture Conversion Within 6 Months, aOR (95% CI)	*P* Value	Microbiological Cure, aOR (95% CI)	*P* Value
Age, y	0.97 (.94–1.01)	.118	0.98 (.94–1.01)	.196
Male sex	0.83 (.38–1.82)	.636	0.44 (.19–1.05)	.064
BMI, kg/m^2	1.10 (.98–1.23)	.116	0.99 (.89–1.11)	.888
COPD	0.33 (.04–3.21)	.342	0.23 (.20–2.64)	.239
Smear positivity	0.65 (.27–1.59)	.347	0.34 (.13–0.86)	.023
Presence of cavity >2 cm	0.85 (.40–1.79)	.665	0.89 (.40–1.99)	.776
Mycobacterium spp				
M avium	Reference		Reference	
M intracellulare	0.58 (.26–1.28)	.177	1.16 (.49–2.75)	.735
Others	0.82 (.30–2.25)	.692	1.62 (.51–5.19)	.416
Clofazimine maintenance dose				
50 mg	Reference		Reference	
100 mg	0.64 (.29–1.42)	.275	1.21 (.52–2.81)	.667

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Clofazimine for MAC-PD treatment

Table 4. Treatment Outcomes According to the Duration of Clofazimine Use

Outcome	<6 Months (n = 27)	6–12 Months (n = 40)	12–18 Months (n = 41)	>18 Months (n = 62)	*P* Value
Culture conversion, No. (%)					
50 mg per day	2 (20.0)	9 (45.0)	14 (70.0)	9 (50.0)	.081
100 mg per day	2 (11.8)	8 (40.0)	14 (66.7)	19 (43.2)	.007
Total	4 (14.8)	17 (42.5)	28 (68.3)	28 (45.2)	<.001
Microbiological cure[a], No. (%)					
50 mg per day	1/9 (11.1)	11/15 (73.3)	11/19 (57.9)	10/18 (55.6)	.030
100 mg per day	5/17 (29.4)	11/16 (68.8)	13/19 (68.4)	22/41 (53.7)	.074
Total	6/26 (23.1)	22/31 (71.0)	24/38 (63.2)	32/59 (54.2)	.002

Open Forum Infect Dis. 2023;11:ofad682.

THANK YOU FOR YOUR ATTENTION