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Original Article

The role of treatment regimen and duration in treating patients with *Mycobacterium avium complex* lung disease: A real-world experience and case—control study

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KEYWORDS
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Abstract *Purpose:* The treatment advantage of guideline-based therapy (GBT) in *Mycobacterium avium complex* lung disease (MAC-LD) is well-known. However, GBT is not always feasible. The aim of the study was to analyze the relationship of treatment regimens and duration with outcomes.
Materials and methods: This study screened patients with MAC-LD from Jan 2011 to Dec 2020 and enrolled those who received treatment. The treatment regimens were categorized to triple therapy (three active drugs) and non-triple therapy. The favorable outcomes included microbiological cure or clinical cure if no microbiologic persistence.
Results: A total of 106 patients with MAC-LD were enrolled. Among them, 88 subjects (83 %) received triple therapy, 58 (54.7 %) had MAC treatment >12 months, and 66 (62.3 %) had favorable outcomes. Patients receiving triple therapy (90.9 % vs. 67.5 %, $p = 0.008$) and treatment >12 months (62.1 % vs. 42.5 %, $p = 0.07$) had higher proportion of favorable outcomes than unfavorable outcomes. Multivariable logistic regression analysis showed that age >65,

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comorbidities of COPD and prior tuberculosis, low hemoglobin, and high MAC burden were independent risk factors of unfavorable outcome. In contrast, triple therapy (OR: 0.018, 95 % CI: 0.04—0.78, $p = 0.022$) and treatment duration >12 months (OR: 0.20, 95 % CI: 0.055—0.69, $p = 0.012$) were protective factors against unfavorable outcome.
Conclusions: Triple therapy including GBT, and treatment more than 12 months achieved more favorable outcome. Maintenance of triple therapy, but not reducing the number of active drugs, might be an acceptable alternative of GBT.

Introduction

Mycobacterium tuberculosis (TB) has a great impact on public health, and the incidence has gradually decreased since the implementation of public health policies, promoting the adequate diagnosis, and treatment of active and latent infection.[1] On the other hand, non-tuberculous mycobacteria (NTM) related infections, especially pulmonary infections, have been increasing worldwide.[2,3] A study in Canada reported a 5-year mortality of 35 %, and the odds rate of mortality was 1.6 compared to the control population.[3] NTM-LD has thus become an important concern because it is possibly associated with poor prognosis. Among NTM-lung diseases (NTM-LD), *Mycobacterium avium complex* lung disease (MAC-LD) is the most common globally, including in the USA[4] and Southeast Asia.[5]

After adequate and timely diagnosis of MAC-LD, treatment may be indicated. Although MAC-LD is considered as indolent and possibly slow in progression, some patients indeed require treatment.[6] Furthermore, some evidence suggests that successful treatment might improve the outcomes of MAC-LD.[7,8]

Current guidelines recommend that the standard anti-MAC regimen should include a combination of a macrolide, rifamycin and ethambutol (guideline-based therapy, GBT) for more than 12 months after sputum conversion.[6] However, adherence to the guidelines has not been consistent. Previous studies reported that only 50—80 % patients received GBT at treatment initiation, and this number fell to 25—40 % at 6 months.[9,10] The main reason might be that the standard anti-MAC treatment is prolonged with cost of adverse effects frequently, and the patients often are fragile. Therefore, the treatments often require modifications, so that it prevents compliance with the recommendations.[11] If any of the drugs of GBT are stopped, then dual therapy or monotherapy with macrolide may lead to macrolide resistance and treatment failure.[9,12] It is plausible to substitute other effective drugs for the components of GBT to maintain the three-drug regimens. There were numerous studies investigating about the efficacy among treatment regimens, mainly comparing different macrolide containing regimens.[13—15] Importantly, few studies have explored the impact of triple therapy on MAC-LD treatment, which combined three active MAC drugs (triple therapy), in contrast to the therapy with less than three active drugs (non-triple therapy). Therefore, we conducted a case—control study at four hospitals in Taiwan to investigate the association of the outcomes with treatment regimens and treatment duration.

Materials and methods

Enrollment of subjects

This case—control study was conducted at four hospitals: two tertiary-care medical centers in Northern Taiwan (National Taiwan University Hospital [NTUH] and Far Eastern Memorial Hospital [FEMH]), one in Central Taiwan (NTUH, Yunlin branch), and one in Southern Taiwan (E-Da Hospital). All patients with MAC-LD from Jan 2011 to Dec 2020 were screened based on the diagnostic criteria of NTM-LD published by ATS/ERS/ESCMID/IDSA in 2020.[16] Patients who received MAC treatment were enrolled in the study.

Clinical data acquisition

Medical records were reviewed to obtain demographic data, co-morbidities, regimens of anti-MAC therapy, treatment outcomes, adverse effects, and relapse occurrences. The information on co-morbidities was recorded at the time of the first isolation of MAC in sputum. The symptoms and laboratory data within 3 months before initiation of anti-MAC treatment were obtained. Sputum smears by Ziehl—Neelsen staining (acid-fast smear, AFS) were reported as trace to four positives according to the diagnostic recommendations.[17] The highest score of AFS within one year before engaging anti-MAC treatment was the maximum AFS score. Maximum AFS scores of sputum smear with trace to 2+ were grouped as weakly positive and those with 3+ or 4+ as strongly positive. The species of mycobacteria were identified by DNA Chip at FEMH and E-Da Hospital and by conventional biochemical methods and MALDI-TOF at NTUH and its Yunlin branch.

Interpretation of radiologic findings

Radiologic findings were reviewed by one pulmonologist and one radiologist. If discrepancies occurred, they discussed them until consensus was reached. MAC-LD was divided into two major types according to radiologic findings: fibro-cavitation (FC) and nodular bronchiectasis

(NB).[18] The severity and extent of radiologic involvement were scored by Brixia scoring system.[19] In brief, each lung was divided into upper, middle, and low lung fields. Each lung field was scored from 0 to 3, according to the extent of radiologic involvement, for a total maximum score of 18. The definitions of other radiologic findings, including tree-in-bud, consolidation, and cavitation, have been described in our previous report.[8]

Treatment regimens and outcomes

The drugs recommended to treat MAC-LD in the 2017 guidelines from the British Thoracic Society were classified as active drugs. They included macrolides (azithromycin or clarithromycin), ethambutol, rifamycin (rifampicin or rifabutin), aminoglycoside (amikacin or streptomycin), fluoroquinolone (FQ) (ciprofloxacin, moxifloxacin or levofloxacin) and isoniazid.[20] The treatment regimens of subjects were categorized according to the first treatment regimen that lasted for three months or more during the early stage of therapy. Favorable outcome was set as microbiological cure or clinical cure if no microbiologic persistence, which was defined according to the recommendations of the NTM-NET consensus of 2018.[21] Namely, the definition of microbiological cure was that none or only one of the cultures showed MAC growth after culture conversion until the end of the anti-MAC therapy.[21] The definition of culture conversion was at least three consecutive negative sputum cultures collected four weeks apart. Clinical cure was defined as clinical and/or radiologic improvement until the end of treatment without obtaining cultures to support microbiological cure.[21] Ineligibility of microbiological and clinical cures was defined as unfavorable outcome, including default and death. Relapse was defined as emergence of at least 2 positive cultures of MAC after treatment completion. The information about mortality was retrieved from medical records till Dec 31, 2022. If no data were available, the default indication was survival.

Statistical analysis

All data are presented as mean $\pm$ standard deviation (SD) for continuous variables and numbers (percentage) for categorial variables. Continuous variables were compared by Mann—Whitney U tests and categorial variables by Chi-squared test. Variables with $p > 0.1$ in univariable analysis were included in multi-variable analysis. To avoid Table 2 fallacies, age, sex, BMI, and cavitation were considered as importantly clinical factors associated with treatment outcome, so these factors were entered into multivariable analysis. The backward input of the logistic regression model was used for multi-variable analysis. Negative conversion and 4-year mortality were compared by Kaplan—Meier analysis and log-rank p tests. Statistical analysis was performed in SPSS version 19 (IBM, Chicago, IL, USA). Statistical significance was set to $p < 0.05$.

Results

Demographic and clinical characteristics of subjects

In the study period, 106 subjects received anti-MAC treatment. Of these, 66 (62.3 %) subjects had favorable outcomes, including 45 (68.2 %) with microbiological cure and 21 (31.8 %) with clinical cure. Age, sex, and BMI were not significantly different between the favorable and unfavorable outcome groups (Table 1). The top three comorbidities were bronchiectasis (46.2 %), prior TB (19.8 %) and COPD (17 %). The rate of COPD was significantly lower in the favorable outcome than in the unfavorable outcome group (10.6 % vs. 27.5 %, $p = 0.036$). In addition, the rates of other chronic airway diseases, including bronchiectasis and prior TB, also tended to be lower in the favorable outcome group (39.4 % vs. 57.5 %, $p = 0.075$, and 13.6 % vs. 30 %, $p = 0.076$, respectively). However, the other comorbidities had similar distributions in the favorable and unfavorable outcome groups.

Compared with the favorable outcome group, the unfavorable outcome group had significantly more subjects with strongly positive AFS [18 (45 %) vs. 13 (19.7 %), $p = 0.021$]. The levels of hemoglobin were significantly higher in the favorable than unfavorable outcome group (12.8 $\pm$ 1.9 vs. 11.9 $\pm$ 1.8, $p = 0.003$). The radiologic patterns and extents of involvement were similar between the favorable and unfavorable outcome groups.

Treatment regimens and duration vs. outcomes

The most common regimen was GBT ($n = 57$, 53.8 %). That was followed by 26 subjects (24.5 %) who were treated with isoniazid, rifamycin and ethambutol (HER) (Table 2). All the regimens had a daily dosing schedule, rather than three-times weekly. The data of the initial and final treatment regimens were shown in Table S1 (in the supplement file). In summary, most of the patients who started with triple therapy (80/88, 90.9 %) finished the treatment with triple therapy. In contrast, some patients who started with non-triple therapy switched to triple therapy (5/18, 27.8 %). Only 8 (7.5 %) subjects had ever received intravenous amikacin. There were no significant differences in individual treatment regimens between the favorable and unfavorable outcome groups. Totally, 88 subjects (83 %) in the study received triple therapy. More subjects in the favorable than in the unfavorable outcome group were treated with triple therapy (60/66, 90.9 % vs. 28/40, 70 %, $p = 0.008$).

The overall rate of adverse effects was 34.9 % (37/106). The top four adverse effects were gastrointestinal side effects (6.6 %, 7/106), dermatologic problems (5.7 %, 6/106), blurred vision (5.7 %, 6/106), and hepatotoxicity (2.8 %, 3/106). Comparing the favorable and unfavorable outcome groups, the treatment durations (393.2 $\pm$ 188.9 vs. 340.5 $\pm$ 245.4 days, $p = 0.22$) and rates of occurrence of adverse effects (33.3 % vs. 37.5 %, $p = 0.68$) were not

Table 1 Demographic characteristics of subjects.

	All (n = 106)	Favorable outcome (n = 66)	Unfavorable outcome (n = 40)	p
Age	61.5 ± 12.7	60.6 ± 13.6	62.9 ± 11.3	0.38
Male	49 (46.2)	27 (40.9)	22 (55)	0.17
BMI (n = 96)	19.6 ± 3.1	19.6 ± 3.0	19.6 ± 3.4	0.96
MAC sets in one year	5.2 ± 3.8	4.8 ± 3.9	6.0 ± 3.5	0.12
Max AFS grade				0.021
Negative	28 (26.4)	20 (30.3)	8 (20)	
Weakly positive	43 (44.3)	33 (50)	14 (35)	
Strongly positive	31 (29.2)	13 (19.7)	18 (45)	
Underlying comorbidities				
DM	8 (7.5)	5 (7.6)	3 (7.5)	1
Hypertension	2 (1.9)	1 (1.5)	1 (2.5)	NA
Heart disease	1 (0.9)	0 (0)	1 (2.5)	NA
CVA	1 (0.9)	0 (0)	1 (2.5)	NA
COPD	18 (17)	7 (10.6)	11 (27.5)	0.036
Prior TB	21 (19.8)	9 (13.6)	12 (30)	0.076
Bronchiectasis	49 (46.2)	26 (39.4)	23 (57.5)	0.075
Cancer	13 (12.3)	8 (12.1)	5 (12.5)	1
CKD	8 (7.5)	4 (6.1)	4 (10)	0.48
ESRD	3 (2.8)	2 (3.0)	1 (2.5)	1
Laboratory				
WBC (n = 95)/mL	7825 ± 3425	7824 ± 3478	7826 ± 3382	0.99
Hb (n = 95) g/dL	12.5 ± 1.9	12.8 ± 1.9	11.9 ± 1.8	0.003
Albumin (n = 95) g/dL	3.9 ± 0.75	4.0 ± 0.72	3.6 ± 0.78	0.10
Symptoms				
Cough	78 (73.6)	49 (74.2)	29 (72.5)	1
Dyspnea	33 (31.1)	19 (28.8)	14 (35)	0.52
Hemoptysis	30 (28.3)	15 (22.7)	15 (37.5)	0.12
Radiographic pattern				
NB	65 (61.3)	40 (60.6)	25 (62.5)	1
FC	33 (31.1)	17 (25.8)	16 (40)	0.14
Cavitation	38 (35.8)	21 (31.8)	17 (42.5)	0.30
Brixia score	5.4 ± 3.1	5.4 ± 3.2	5.4 ± 3.1	0.99

Data are presented as mean ± standard deviation or number (percentage).
Abbreviations: AFS: acid-fast smear; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CVA: cerebrovascular accidence; DM: diabetes mellitus; ESRD: end stage renal disease; FC: fibro-cavitation; Hb: hemoglobin; MAC: *Mycobacterium avium* complex; NB: nodular bronchiectasis; TB: tuberculosis; WBC: white blood cells.

significantly different. However, there were less subjects with adjusting treatment regimens within the first three months in the favorable outcome group, compared to unfavorable outcome [9.1 % (6/66) vs. 22.5 % (9/40), p = 0.083]. Besides, the favorable outcome group tended to have more subjects with treatment duration >12 months than the unfavorable outcome group [62.1 % (41/66) vs. 42.5 % (17/40), p = 0.070].

For patients with negative culture conversion of microbiology (42.5 %, 45/106) in the total study population, more than half of negative conversions (55.6 %) were achieved within 120 days of treatment (Fig. 1). The Kaplan—Meier analysis of negative conversion within 360 days showed that triple therapy more likely had negative conversion than non-triple therapy (log rank p = 0.047) (Fig. 2).

Risk analysis of unfavorable outcome

Logistic regression showed COPD [odds ratio (OR): 2.51, 95 % confidence interval (CI): 1.06—5.95, p = 0.036], low hemoglobin (OR: 1.28 per g/dl decrement, 95 % CI:1.02—1.62, p = 0.034) and strongly positive AFS (OR: 1.76, 95 % CI: 1.07—2.88, p = 0.035) to be the risk factors of unfavorable outcome in uni-variable analysis (Table 3). Triple therapy was found to be a protective factor against unfavorable outcome (OR: 0.77, 95 % CI: 0.62—0.96, p = 0.008). Multi-variable analysis showed age >65 (OR: 4.02, 95 % CI: 1.10—14.75, p = 0.036), low hemoglobin (OR: 1.64 per g/dl decrement, 95 % CI: 1.17—2.28, p = 0.004), COPD (OR: 5.00, 95 % CI: 1.09—22.96, p = 0.038), prior TB (OR: 6.24, 95 % CI: 1.51—25.80, p = 0.011) and strongly positive AFS (OR: 5.93, 95 % CI: 1.42—24.72, p = 0.014) were risk factors of unfavorable outcome. Treatment for more than 12 months and triple therapy were protective factors against unfavorable outcome (OR: 0.20, 95 % CI: 0.055—0.69, p = 0.012, and OR: 0.18, 95 % CI: 0.040—0.78, p = 0.022, respectively). If subjects who died within one year after initiating treatment was excluded to avoid the bias, OR of treatment more than 12 month to unfavorable outcome was 0.50 (95 % CI: 0.22—1.13, p = 0.095). The

Table 2 Treatment regimens and outcome.

	All (n = 106)	Favorable outcome (n = 66)	Unfavorable outcome (n = 40)	p
Regimen				
GBT	57 (53.8)	38 (57.6)	19 (47.5)	0.32
M-RIF	3 (2.8)	2 (3.0)	2 (2.5)	1
M-EMB	6 (5.7)	2 (3.0)	4 (10)	0.20
M-FQ	6 (5.7)	2 (3.0)	4 (10)	0.20
HER	26 (24.5)	19 (28.8)	7 (17.5)	0.25
IV amikacin	8 (7.5)	7 (10.6)	1 (2.5)	0.25
Others	8 (7.5)	3 (4.5)[a]	4 (10)[b]	
Triple therapy	88 (83.0)	60 (90.9)	27 (67.5)	0.008
Adjusting regimen in the first 3 months	15 (14.2)	6 (9.1)	9 (22.5)	0.083
Side effects	37 (34.9)	22 (33.3)	15 (37.5)	0.68
Treatment duration	373.3 ± 212.4	393.2 ± 188.9	340.5 ± 245.4	0.22
Treatment >12 months	58 (54.7)	41 (62.1)	17 (42.5)	0.070
Death in 4 years	10 (9.4)	3 (4.5)	7 (17.5)	0.063

[a] 2 were rifampin, moxifloxacin, and clarithromycin; 1 was azithromycin, ethambutol, and moxifloxacin.
[b] 1 was rifampin, moxifloxacin, and clarithromycin; 1 was levofloxacin monotherapy; 1 was rifampin and ethambutol; 1 was rifampin and levofloxacin.
Data are presented as mean ± standard deviation or number (percentage).
Abbreviations: GBT: guideline-based therapy; IV: intravenous; M-EMB: macrolide plus ethambutol; M-FQ: macrolide plus fluroquinolone; M-RIF: macrolide plus rifamycin.

results of multi-variable analysis for factors associated with treatment outcome were similar to those in total subjects (Table S2).

Subgroup analysis for the triple therapy on treatment outcome

The association between triple therapy and treatment outcome was analyzed by subgroup (Fig. 3). The results showed that triple therapy against unfavorable outcome was present in treatment for more than 12 months and the possible prognostic factors, including sex, age, BMI, the symptom of hemoptysis, maximum sputum AFS scores, cavitation, chronic lung disease, and prior TB.

Treatment vs. mortality

Favorable/unfavorable outcomes seemed to correlate with 4-year mortality. The 4-year mortality of the favorable outcome group was 4.5 % (3/66). In contrast, the 4-year mortality rate of the unfavorable outcome group was 17.5 % (7/40); however, the difference of 4-year mortality between the two groups was not significant (p = 0.063) (Table 2). On the other hand, Kaplan–Meier survival analysis showed triple therapy to be associated with better 4-year survival than was non-triple therapy (log rank p = 0.032) (Fig. 4).

Recurrence after favorable outcome

The recurrence rate of MAC after a favorable outcome was 22.7 % (15/66), with recurrence 432.5 ± 411.2 days after the completion of anti-MAC treatment; thus, it was not associated with the first 3-month treatment regimen or treatment duration. The risk factors of recurrence were age >65 (OR: 3.67, 95 % CI: 1.09–12.39, p = 0.04) and COPD (OR: 5.58, 95 % CI: 1.09–28.60, p = 0.05).

Discussion

The present study found that unfavorable treatment outcomes of MAC-LD were not uncommon (37.7 %). Triple anti-MAC therapy, including GBT, and treatment length >12 months were significantly associated with favorable outcomes. In addition, age >65, high bacteria burden, low hemoglobin, and comorbidities of COPD and prior TB were the other risk factors for unfavorable outcomes of MAC-LD treatment, according to multi-variable logistic regression. Furthermore, after achieving favorable outcome, MAC-LD had a recurrence rate of 22.7 %.

GBT-related adverse effects are one main concern of adherence to the NTM treatment guidelines. Previous studies from various countries have reported that around 50–80 % of patients with MAC-LD receive GBT, whereas others are treated with dual therapy or monotherapy with macrolide.[9–11,22,23] In addition, a study based on US Medicare data reported that the rate of GBT therapy at initiation was around 50 % but fell to only 5–8% at one-year treatment.[10] There are two options to overcome the issue of treatment-related adverse effects: stop one or more drugs of GBT, or substitute one of the drugs with another. Though dual therapy with macrolide and ethambutol has been reported as an alternative to GBT in previous studies,[24,25] some dual therapies or monotherapy with macrolide were reportedly associated with acquired macrolide resistance and treatment failure.[12] The present study found that triple therapy, including GBT had benefits on favorable outcome, 4-year mortality, as well as sputum negative conversion within 12 months. It also showed that the benefits of triple therapies were present in all

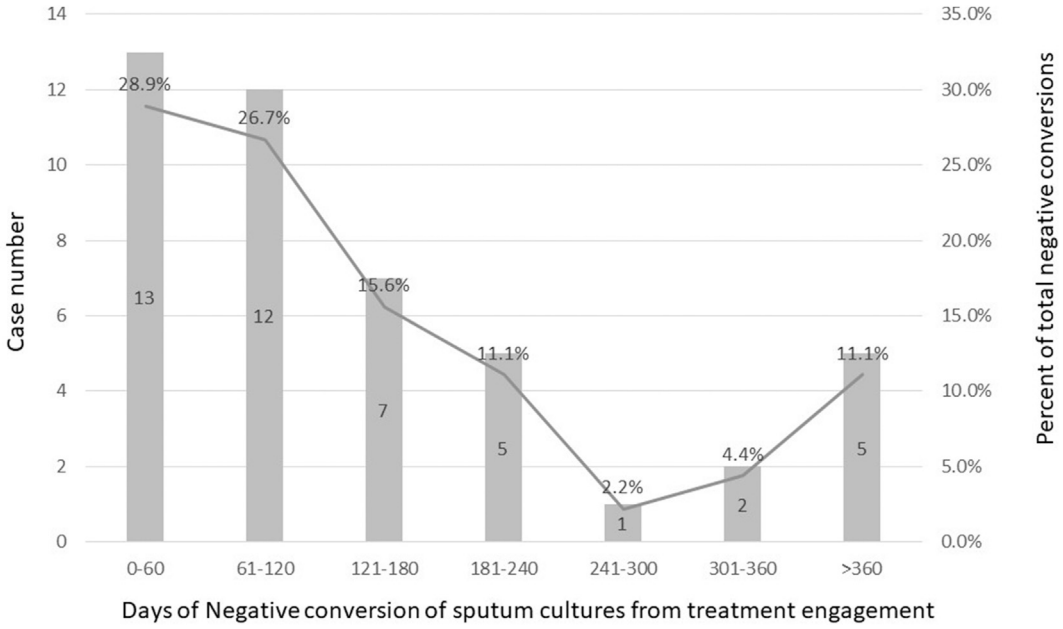

Figure 1. For patients with negative culture conversion of microbiology, more than half of negative conversions (55.6 %) were achieved within 120 days of treatment.

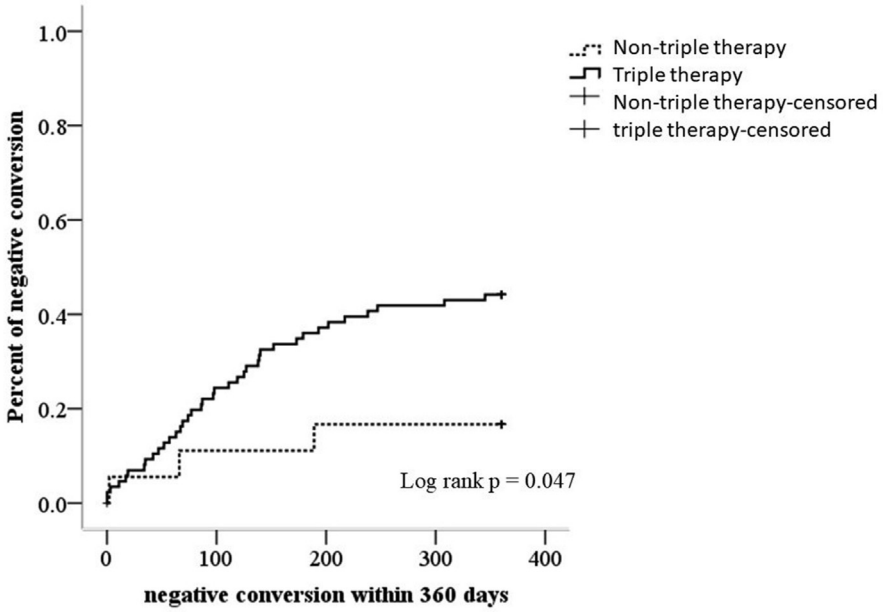

Figure 2. The Kaplan—Meier analysis of negative conversion within 360 days showed that triple therapy more likely had negative conversion than non-triple therapy (log rank $p = 0.047$).

importantly prognostic factors. The guidelines highlight the importance of GBT, especially macrolide.[16] However, this finding suggested that triple therapy might be one of the key principles in need of adjusting MAC-LD, if GBT is not feasible.

The non-GBT triple therapy regimen of the present study was mainly composed of isoniazid, rifamycin and ethambutol (HER). HER has long been known as an effective anti-MAC treatment regimen.[18,26,27] Therefore, the guidelines of BTS in 2017 allowed isoniazid to be substituted for macrolide or added on in cases of macrolide resistant MAC-LD.[20] One reason of HER use might be that anti-TB treatment commences immediately if sputum AFS is positive, out of concern for public health, especially in the absence of prompt molecular studies. Even if MAC is confirmed microbiologically one to two months later, HER might be maintained if there are clinical or radiologic improvement and acceptable adverse effects.[28]

The guidelines on MAC treatment recommend a duration of at least 12 months after sputum conversion.[6,20] Treatment for a longer duration might decrease the recurrence rate[15] and subsequent mortality rate.[7] In our study, treatment duration of more than 12 months was associated with favorable treatment outcome. Some studies have proposed

Table 3 Odds ratios of unfavorable outcome.

	Crude OR	*p*	Adjusted OR	*p*
Sex (male)	1.77 (0.80–3.90)	0.17		
Age (>65)	0.99 (0.96–1.02)	0.37	4.02 (1.10–14.75)	0.036
BMI (<18.5)	1.00 (0.88–1.15)	0.96		
Max AFS				
Negative	Reference		Reference	
Weakly positive	1.02 (0.70–1.49)	1	2.49 (0.56–11.15)	0.23
Strongly positive	1.76 (1.07–2.88)	0.035	5.93 (1.42–24.72)	0.014
Hb (per g/dl decrement)	1.28 (1.02–1.62)	0.034	1.64 (1.17–2.28)	0.004
Cavitation	1.34 (0.81–2.21)	0.30		
Bronchiectasis	1.46 (0.98–2.18)	0.075		
COPD	2.51 (1.06–5.95)	0.036	5.00 (1.09–22.96)	0.038
Prior TB	2.15 (1.00–4.64)	0.076	6.24 (1.51–25.80)	0.011
Treatment >12 months	0.68 (0.46–1.03)	0.070	0.20 (0.055–0.69)	0.012
Triple therapy	0.77 (0.62–0.96)	0.008	0.18 (0.040–0.78)	0.022
Adjusting regimens in the first 3 months	2.91 (0.95–8.93)	0.083		

Data are presented as mean (95 % confidence interval).
Abbreviations: AFS: acid-fast smear; BMI: body mass index; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; TB: tuberculosis.

that 15 or 18 months of treatment after sputum conversion might further decrease recurrence and improve outcomes in selected patients.[29,30] However, adverse effects often accompany with prolonged treatment durations and hinder the treatment. Data from the United States, the Netherlands, and Germany have shown that 5–25 % of patients maintain anti-MAC treatment for one year.[10,23,31] In addition, some patients with good clinical response do not complete the targeted lengthy treatment period, and microbiological cure cannot be achieved due to a lack of sputum production. Therefore, individual goals of MAC-LD treatment may be set by the patients themselves, despite healthcare professionals' efforts to comply with the recommendations in the contemporary guidelines.[6,20] Further study will be needed to focus on different treatment goals in subgroups with different disease statuses and treatment responses.

Numerous studies have investigated the risk factors of MAC-LD treatment failure and poor outcomes.[32–34] The present study echoed the findings of previous studies that age >65, high bacteria burden, and low hemoglobin were risk factors for unfavorable outcomes.[32–34] The study in Japan showed that fewer old patients received triple therapies, and more were treated with dual therapies.[35] Such patterns of treatment might further enhance the negative effects on treatment outcomes in older adults. A narrative review also stated that patients with MAC-LD without chronic lung disease have more sputum conversion than do those with chronic lung disease.[36] The effects of chronic lung diseases such as prior TB and COPD on unfavorable outcomes were observed in the present study. Bronchiectasis did not significantly affect treatment outcome in the present study, but uni-variable analysis showed the trend associated with unfavorable outcomes. Cavitation and extensive radiologic involvement have also been reported as risk factors in previous studies.[8,33,34] It was plausible that patients with MAC-LD with cavitation and extensive disease involvement prefer to commence MAC-LD treatment. Therefore, it might weaken the impact on treatment outcome in view of the population undergoing MAC-LD treatment.

This study has some limitations. First, the number of subjects was limited, even though data covering a period of 10 years were retrieved from four hospitals. In addition, there were some missing data in the retrospective study, which may bias the results. Second, the information on the species of MAC and the status of macrolide resistance were not available because of laboratory limitations. Some evidence suggests that *Mycobacterium intracellulare* is more virulent than *Mycobacterium avium*.[37] The MAC species related outcome difference might have biased the present study. Regarding macrolide resistance, only 5 % of patients with MAC with treatment naïve had macrolide resistance in Taiwan,[38] which might minimize the influence of macrolide resistance on the present study. Third, it is not rare to adjust treatment regimens during the treatment course. The current study assumed that the treatment regimens for three months or more at the early stage represented as the whole treatment regimen. It may introduce bias and overestimate the efficacy of triple therapy. Fourth, patients diagnosed in 2019 and 2020 would have been censored before the 4-year point, which may have the impact on the valid comparison of 4-year survival rates. Fifth, we adopted either clinical cure or microbiologic cure as favorable outcome in the current study, instead of negative culture lasting for at least 12 months after initiating treatment. It might inflate the efficacy of triple therapy. However, it reflected the real-world practice, and we investigated the relation between treatment more than 12 months and outcome to reduce the prejudice. Lastly, the present study was conducted at four hospitals in Taiwan. Before generalization to other areas or ethnicities, the findings of this study will need to be validated in large-scale prospective studies.

In conclusion, MAC-LD remains difficult to treat, and the unfavorable outcome rate was as high as 37.7 % in the present study. Among the treatment strategies, triple therapy and treatment duration >12 months were

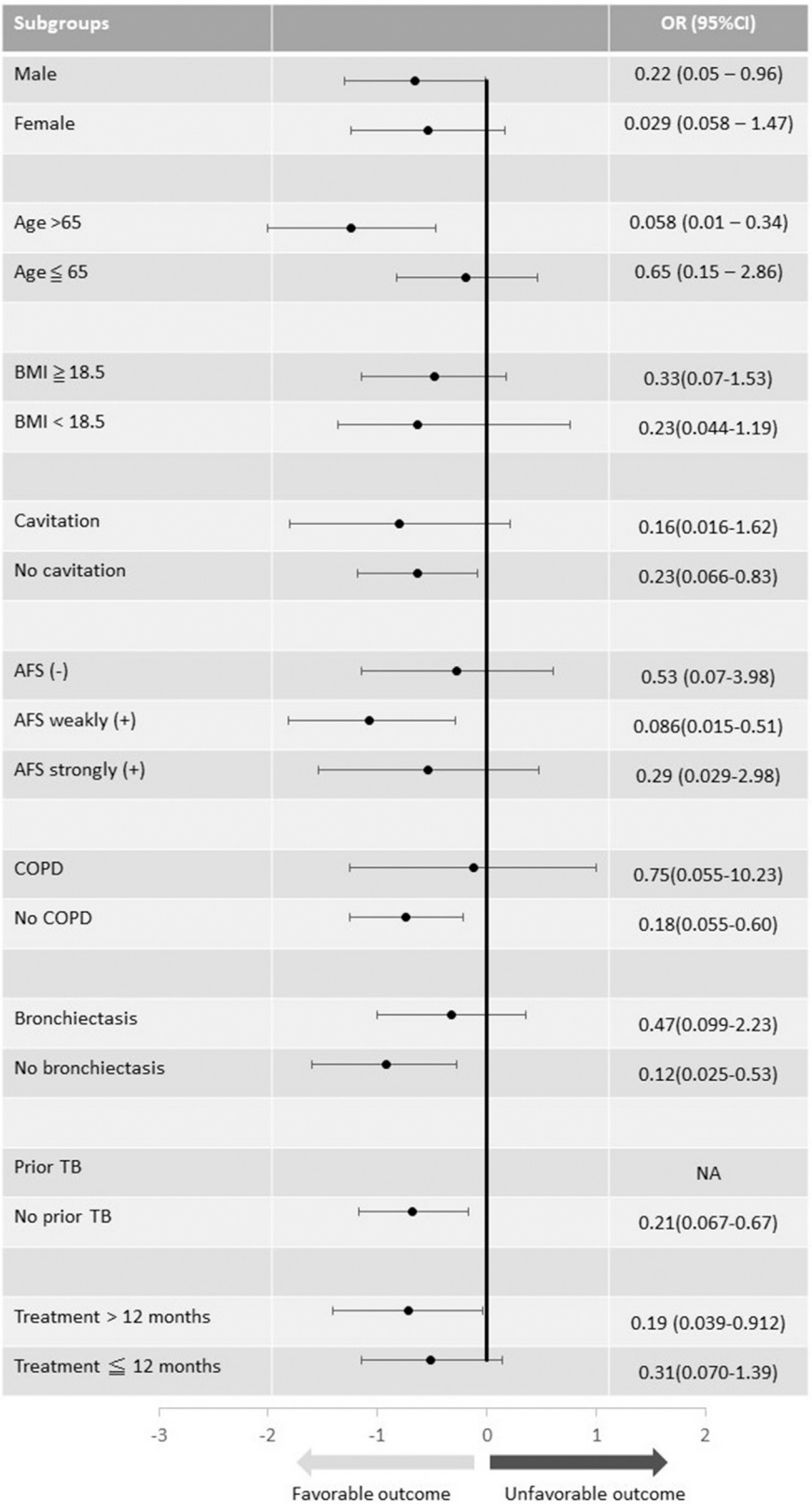

Figure 3. Triple therapy against unfavorable outcome was present in treatment for more than 12 months and the possible prognostic factors, including sex, age, BMI, the symptom of hemoptysis, maximum sputum AFS scores, cavitation, chronic lung disease, and prior TB.

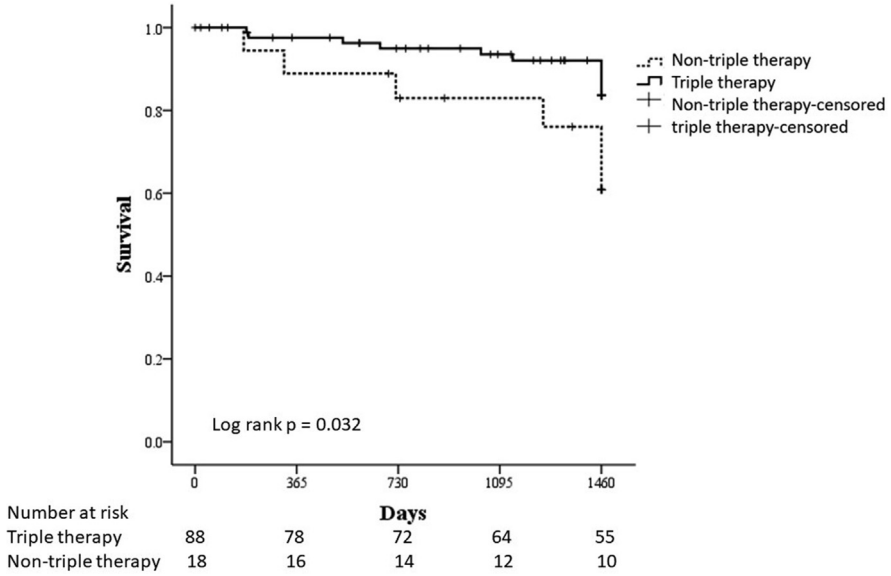

Figure 4. Triple therapy was associated with better 4-year survival than non-triple therapy (log rank $p = 0.032$).

significantly associated with favorable outcomes in treating MAC-LD. Notably, triple therapy, including GBT, were associated with not only short-term favorable outcomes but also 4-year mortality in MAC-LD. Although age, NTM bacteria burden, and comorbidities of COPD and prior TB were associated with unfavorable outcome of MAC-LD, maintenance of triple therapy for at least 12 months, but not reducing the number of drugs may be an alternative if GBT cannot be tolerated.

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Ethical approval and consent to participate

The study was approved by the Institutional Review Boards of the attending hospitals (ID201009046/FEMH-107062-E and 201704001RINB), and informed consent was waived due to the retrospective design.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contribution

Shu CC was responsible for the conception, design, data collection, and critical review. Wang PH was involved in data collection and analysis. Wang PH and Shu CC prepared and wrote the manuscript. Chen YU, Wei YF, and Cheng SL were responsible for data collection and critical review.

Conflicts of interest

All of the authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.11.006.