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Original Article

The impact of nontuberculous mycobacterial lung disease in critically ill patients: Significance for survival and ventilator use

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Abstract *Background:* This study investigates the impact of nontuberculous mycobacterial lung disease (NTM-LD) on mortality and mechanical ventilation use in critically ill patients.
Methods: We enrolled patients with NTM-LD or tuberculosis (TB) in intensive care units (ICU) and analysed their association with 30-day mortality and with mechanical ventilator-free survival (VFS) at 30 days after ICU admission.
Results: A total of 5996 ICU-admitted patients were included, of which 541 (9.0 %) had TB and 173 (2.9 %) had NTM-LD. The overall 30-day mortality was 22.2 %. The patients with NTM-LD had an adjusted hazard ratio (aHR) of 1.49 (95 % CI, 1.06—2.05), and TB patients had an

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aHR of 2.33 (95 % CI, 1.68—3.24), compared to ICU patients with negative sputum mycobacterial culture by multivariable Cox proportional hazard (PH) regression. The aHR of age<65 years, obesity, idiopathic pulmonary fibrosis, end-stage kidney disease, active cancer and autoimmune disease and diagnosis of respiratory failure were also significantly positively associated with ICU 30-day mortality. In multivariable Cox PH regression for VFS at 30 days in patients requiring invasive mechanical ventilation, NTM-LD was negatively associated with VFS (aHR 0.71, 95 % CI: 0.56—0.92, $p = 0.009$), while TB showed no significant association. The diagnosis of respiratory failure itself predicted unfavourable outcome for 30-day mortality and a negative impact on VFS at 30 days.

Conclusions: NTM-LD and TB were not uncommon in ICU and both were correlated with increasing 30-day mortality in ICU patients. NTM-LD was associated with a poorer outcome in terms of VFS at 30 days.

Introduction

Nontuberculous mycobacteria (NTM) are present in the environment, and over 200 recognized species of NTM have been identified using molecular techniques.[1,2] The incidence of NTM lung disease (NTM-LD), the most common site of NTM infection, has been on the rise in recent decades.[3,4] The majority of NTM-LD is caused by the *Mycobacterium avium-intracellulare complex* (MAC) and the *Mycobacterium abscessus* complex, with other species causing only a small proportion of NTM-LD.[5] This increase can be attributed to a variety of factors, including an aging population with multiple health issues, greater awareness of NTM-LD, and advancements in NTM identification, as well as outbreaks acquired in hospital settings.[2,6—8]

For clinical illness, NTM-LD exhibits a spectrum of disease pathogenicity that ranges from being innocuous to causing severe illness.[1] In fact, the prognosis is variable, and the success rate of NTM treatment is only around 50—60 %.[9,10] In a general NTM-LD cohort, the overall mortality at 8 years was around 35 %.[11] By contrast, there is a paucity of data on the clinical outcomes of NTM-LD patients admitted to the ICU, highlighting the need for further investigation in this population.

Several previous studies have demonstrated a high in-hospital mortality rate among critically ill patients with active tuberculosis (TB) or those requiring invasive mechanical ventilation, ranging from 62.7 % to 65.9 %.[12,13] Only one study reported a high mortality rate among patients with NTM-LD, with a 100-day mortality rate reaching up to 47 %.[14] However, these previous studies on NTM-LD have not been validated, were limited by small sample sizes, and lacked comprehensive information on the utilization of mechanical ventilation. Therefore, further research is necessary to obtain a comprehensive understanding of the clinical relevance and prognostic impact of NTM-LD compared to TB, especially in terms of survival and the utilization of mechanical ventilation in critically ill patients.

Methods

Study design and setting

This study was a retrospective analysis of de-identified clinical data from the period from January 2006 to March 2022 collected at the National Taiwan University Hospital (NTUH) and its Hsin-Chu and Yun-Lin branches in Taiwan. We recruited participants and data from the National Taiwan University Hospital-Integrative Medical Database (NTUH-iMD), a hospital database that contains all medical records for patients at NTUH. This database is regularly updated with death information from the government notification system of the Ministry of Health and Welfare of Taiwan. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (NO: 201704001RINB) and informed consent was waived due to the retrospective study design and the use of de-identified patient data.

The aim of our study was to evaluate the effect of lung disease caused by mycobacteria, including NTM-LD and TB, on 30-day mortality after admission to the ICU. The secondary objective was to assess the 30-day mechanical ventilation-free survival in patients who received invasive mechanical ventilation.

Identification of index cases and group definition

To assess the impact of NTM-LD during ICU admission, we classified patients into three groups. The first group, referred to as NTM-LD, consisted of individuals who had at least two sputum cultures yielding the same species of NTM or one positive NTM result from a bronchoscopic specimen according to microbiological criteria of diagnostic guideline recommended by American Thoracic Society.[1] In cases where the subject was defined by a minimum of two sputum cultures, there had to be no more than three consecutive negative mycobacterial isolation results or any isolation of a different NTM species between the two

sputum cultures. The second group, referred to as the TB group, was composed of patients with positive isolation of *Mycobacterium tuberculosis* from airway specimens or those diagnosed with pulmonary tuberculosis through clinical, radiographic and pathological examination. The third group, referred to as the control group, consisted of patients without any isolated mycobacterial species. It is important to note that a patient could not be classified into more than one patient group. The patients with ICU admission, who met the NTM-LD criteria and the TB group criteria, were excluded from NTM-LD group.

The selected patient groups overlapping the ICU admission were defined as follows: In the NTM-LD group, the time period between the first and last specimens of the same NTM species overlapped with the interval between 90 days prior to the ICU admission day and the ICU discharge day. In the TB group, the time period between the first positive TB specimen or clinical diagnosis and the following 180 days overlapped with the interval between 90 days prior to the ICU admission day and the ICU discharge day. In the control group, the time period between the first and last specimens of negative mycobacteria overlapped with the interval between 90 days prior to the ICU admission day and the ICU discharge day (as Fig. S1 in the supplementary file).

Data collection and outcome

Data pertaining to known risk factors or potential confounding factors for mycobacterial infection were collected. The details and definitions of these comorbidities are documented in the supplementary file (Table S1). The use of anti-mycobacterial agents was defined as the cumulative prescription of 28 days within a 91-day period (equivalent to 13 weeks), either as a single agent or in combination. The category of anti-mycobacterial agents was defined according to ATS/IDSA guideline, including fluoroquinolones, macrolides, and aminoglycosides.[8]

The primary objective was to determine the 30-day mortality rate following ICU admission. The death of patients was verified on the NTUH-iMD by linking to the national death notification system from the Ministry of Health and Welfare of Taiwan. The secondary objective was to assess the mechanical ventilation-free survival rate within 30 days for patients who received invasive mechanical ventilation. This was defined as the number of days that patients survived after liberation from mechanical ventilation within 30 days after ICU admission.[15]

Statistical analysis

All statistical analyses were performed in the SAS 9.4 statistical software package for Windows (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value of less than 0.05 was considered statistically significant. Comparisons between patient groups were conducted using chi-squared tests for categorical variables and Student's t-tests for continuous variables. Univariate Cox proportional hazard (PH) regression analysis was employed to calculate the crude hazard ratios (HRs) for factors of interest, using 30-day ICU mortality as the outcome. Multivariable Cox PH regression analysis was then performed, using the same outcome, with predictor variables that had p-values of less than 0.05 in the univariate analysis being entered into the model. We employed the supremum test to examine the proportional hazards assumption in the Cox proportional hazards models. For factors that violated this assumption, we introduced an interaction term between the factor and follow-up time, as guided by previous literature.[16] The 30-day mechanical ventilation-free survival was analysed in a similar manner using Cox PH. The survival curves were compared using the log-rank test.

We also conducted two sensitivity analyses to determine the impact of Mycobacterial infection. The first analysis included patients with APACHE II scores at the time of ICU admission, with the caveat that these scores are only available in our database from 2010 onwards. The second sensitivity analysis was aimed at patients diagnosed after their ICU admission. This specifically involved examining the 30-day mortality post—index day, calculated from the date of ICU admission for those diagnosed with TB/NTM-LD before ICU admission, and from the date of TB/NTM-LD diagnosis for those diagnosed after ICU admission.

Results

Patient characteristics

Of the 82,325 patients who had respiratory specimens for mycobacterial cultures at our hospital between January 2006 and March 2022, 52,606 met the definitions for NTM-LD, TB, and control groups. Among these patients, 5996 had ICU admission either just prior to or immediately after the mycobacterial survey. The cohort included 173 patients with NTM-LD and 541 patients with TB, and a flow diagram of the cohort is depicted in Fig. 1. The 30-day mortality rate was 22.2 %, and the mean length of stay in the ICU was 16.4 $\pm$ 19.2 days. The 30-day mortality rates after ICU admission were 26.01 % (45/173) in the NTM-LD group, 25.69 % (139/541) in the TB group, and 21.7 % (1146/5282) in the control group.

The patient characteristics are presented in Table 1. The NTM-LD group was found to be older and to have more cavitary lesions in comparison with the control group. Both the NTM-LD and TB groups had lower body mass indices as well as lower prevalence of metabolic comorbidities such as heart failure ($p = 0.002$, significantly different in TB vs. control) and diabetes mellitus ($p < 0.001$, significantly different in NTM-LD vs. control). Compared with the control group, patients with NTM-LD had more underlying respiratory disease ($p < 0.001$), such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF). Additionally, fewer patients in the NTM-LD and TB groups had a diagnosis of kidney disease or active cancer ($p < 0.001$ and $p = 0.003$, respectively). Fewer patients with pulmonary TB were coded with other pulmonary infections, including pneumonia, lung abscess, or empyema. Within our cohort, fewer patients presenting with NTM-LD or TB exhibited respiratory failure in comparison with the control group ($p < 0.001$, both).

In regard to NTM species, the NTM-LD patients were infected with MAC at a rate of 43.9 %, followed by *M. abscessus* (30.1 %), *Mycobacterium kansasii* (13.3),

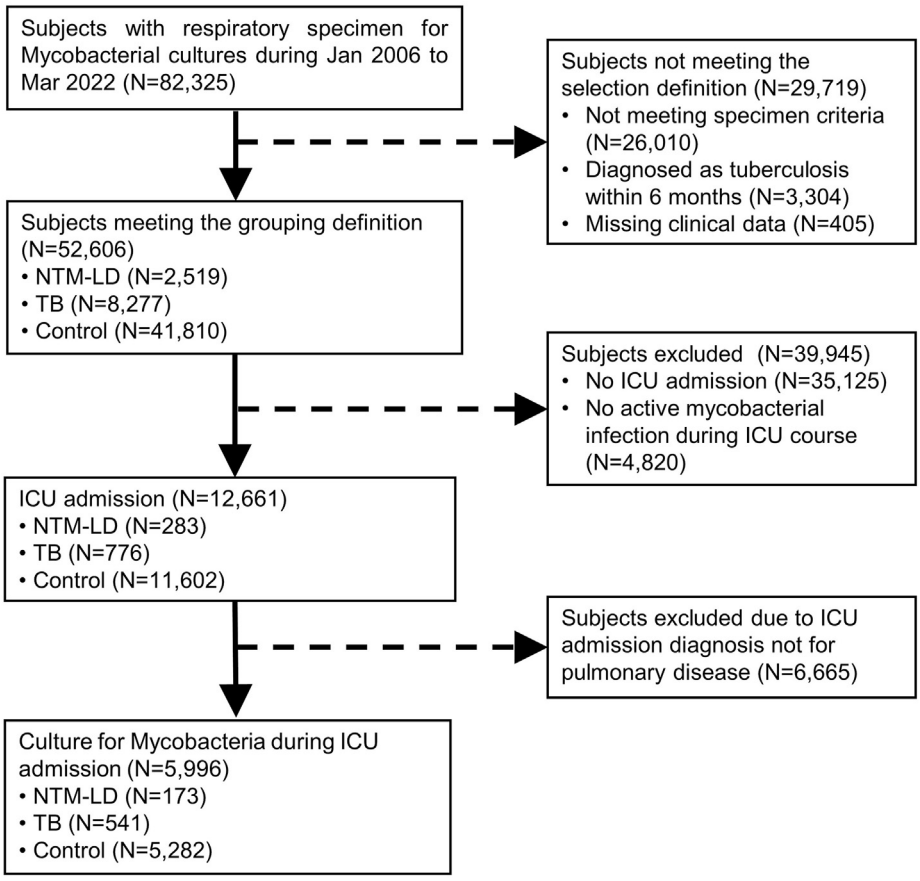

Fig. 1. Flow diagram of the cohort. The diagram shows the numbers of individuals (N) excluded at different stages and the identification of cases for the main end points.

Mycobacterium fortuitum (6.4 %), *Mycobacterium chelonae* (1.7 %) and *Mycobacterium gordonae* (1.7 %) (Table S2 provided in the supplementary file).

For anti-mycobacterial treatment in our enrollees, there was 162 NTM-LD and 511 TB patients received the effective treatment, respectively. Among them, 8.64 % (n = 14) patients with NTM-LD who were exposed to anti-mycobacterial agents before ICU admission, compared to 32.29 % (n = 165) patients with TB.

Outcome analyses of 30-day mortality

Table 2 presents the results of the univariate and multivariate Cox regression analysis aimed at identifying factors associated with 30-day mortality. In the multivariate Cox regression analysis, patients in the NTM-LD and TB groups were found to have a significantly increased adjusted hazard ratio (aHR) of 1.49 (95 % CI, 1.06—2.05, $p = 0.015$) and 2.33 (95 % CI, 1.68—3.24, $p < 0.001$), respectively, compared with the control group. Comorbidities such as overweight, obesity, IPF, kidney disease, end-stage kidney disease (ESKD), active cancer, and autoimmune disease were found to be independent factors associated with increased 30-day mortality, while COPD, asthma and diabetes were identified as protective factors.

The log-rank test revealed no statistically significant differences in 30-day mortality or mechanical ventilation-free survival between various NTM species (for details, see Table S3 and Table S4 in the supplementary file). The *p* values of the comparisons between MAC and *M. abscessus* were 0.136 for 30-day mortality and 0.69 for ventilation-free survival at 30 day.

Through both univariate and multivariable Cox regression analyses for 30-day mortality, it was found that patients with TB who initiated anti-mycobacterial agents before ICU admission had a greater benefit compared to those who started treatment after ICU admission or received no treatment, with an aHR of 0.64 (95 % CI: 0.42—0.97, $p = <0.001$). However, this beneficial effect of anti-mycobacterial treatment before ICU admission was not observed in patients with NTM-LD with an aHR of 0.36 (95 % CI: 0.05—2.87, $p = 0.336$) (for details, see Table S6 in the supplementary file).

Outcome analyses of 30-day ventilator free survival

Our secondary objective was to identify the factors associated with survival without mechanical ventilation at 30 days. A total of 4506 patients who required mechanical ventilation were included for further analysis. The rates of survival without mechanical ventilation at 30 days were 54.62 % (65/119) in the NTM-LD group, 59.78 % (217/363) in the TB group, and 64.59 % (2599/4024) in the control group, respectively (for detailed demographics, see Table S3). The results of both univariate and multivariable Cox regression analysis are presented in Table 3. The analysis demonstrated that

Table 1 Basic demographics of study population.

Variables	All N = 5996	NTM-LD N = 173	TB N = 541	Control N = 5282	*p*-value
Age, ≥65 years	3972 (66.24 %)	131 (75.72 %)[a]	367 (67.84 %)	3474 (65.77 %)	0.017
Sex, male	3876 (64.64 %)	122 (70.52 %)	375 (69.32 %)	3379 (63.97 %)	0.012
BMI (kg/m2) (N = 5565)					<0.001[a,b]
Underweight (BMI < 18.5)	1010 (18.2 %)	50 (30.86 %)	128 (25.05 %)	832 (17.07 %)	
Normal weight (18.5 ≤ BMI < 24)	2763 (49.80 %)	84 (51.85 %)	296 (57.93 %)	2383 (48.88 %)	
Overweight (24 ≤ BMI < 27)	1029 (18.55 %)	13 (8.02 %)	65 (12.72 %)	951 (19.51 %)	
Obesity (27 ≤ BMI)	746 (13.45 %)	15 (9.26 %)	22 (4.31 %)	709 (14.54 %)	
Ever smoke (N = 5969)	2228 (37.33 %)	64 (36.99 %)	211 (39.22 %)	1953 (37.14 %)	0.635
Cavity lesion	402 (6.7 %)	19 (10.98 %)[a]	49 (9.06 %)[b]	334 (6.32 %)	0.004
Underlying disease					
Sinusitis	42 (0.7 %)	3 (1.73 %)	3 (0.55 %)	36 (0.68 %)	0.240
COPD	1146 (19.11 %)	67 (38.73 %)[a]	93 (17.19 %)	986 (18.67 %)	<0.001
Asthma	302 (5.04 %)	14 (8.09 %)	20 (3.7 %)	268 (5.07 %)	0.066
Bronchiectasis	174 (2.9 %)	26 (15.03 %)[a]	12 (2.22 %)	136 (2.57 %)	<0.001
IPF	305 (5.09 %)	25 (14.45 %)[a]	21 (3.88 %)	259 (4.9 %)	<0.001
Heart failure	1379 (23 %)	38 (21.97 %)	92 (17.01 %)[b]	1249 (23.65 %)	0.002
Diabetes mellitus	2069 (34.51 %)	40 (23.12 %)[a]	160 (29.57 %)	1869 (35.38 %)	<0.001
Kidney disease	2105 (35.11 %)	41 (23.7 %)[a]	151 (27.91 %)[b]	1913 (36.22 %)	<0.001
ESKD	77 (1.28 %)	3 (1.73 %)	7 (1.29 %)	67 (1.27 %)	0.866
GERD	408 (6.8 %)	21 (12.14 %)[a]	43 (7.95 %)	344 (6.51 %)	0.008
Cirrhosis	14 (0.23 %)	0 (0.00 %)	2 (0.37 %)	12 (0.23 %)	0.656
Active cancer	1726 (28.79 %)	39 (22.54 %)[a]	128 (23.66 %)[b]	1559 (29.52 %)	0.003
Autoimmune disease	266 (4.44 %)	11 (6.36 %)	32 (5.91 %)	223 (4.22 %)	0.088
Post transplant	104 (1.73 %)	2 (1.16 %)	13 (2.4 %)	89 (1.68 %)	0.400
ICU diagnosis					
Pulmonary infections[c]	3908 (65.18 %)	122 (70.52 %)	213 (39.37 %)[b]	3573 (67.64 %)	<0.001
Respiratory failure	3657 (60.99 %)	97 (56.07 %)[a]	209 (38.63 %)[b]	3351 (63.44 %)	<0.001

[a] $p < 0.05$ as comparison between NTM-LD with control group.
[b] $p < 0.05$ as comparison between TB with control group.
[c] Pulmonary infection including pneumonia, lung abscess, or empyema.
NTM-LD non-tuberculous mycobacterial pulmonary disease, *TB* tuberculosis, *BMI* Body mass index, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *ESKD* end stage kidney disease, *GERD* gastroesophageal reflux disease.

patients with NTM-LD (aHR of 0.71, 95 % CI: 0.56—0.92, $p = 0.009$), advanced age (≥65 years) (aHR of 0.92, 95 % CI: 0.84—0.99, $p = 0.031$), IPF (aHR of 0.75, 95 % CI: 0.63—0.9, $p = 0.002$), history of kidney disease (aHR of 0.77, 95%CI: 0.71—0.84, $p < 0.001$), active cancer (aHR of 0.8, 95 % CI: 0.74—0.88, $p < 0.001$), or ICU diagnosis of respiratory failure (aHR of 0.76, 95 % CI: 0.7—0.82, $p < 0.001$) were associated with significantly decreased mechanical ventilation-free survival. Conversely, male sex, asthma and diabetes were linked with statistically significant increases in mechanical ventilation-free survival, as indicated by aHR of 1.1 (95 % CI: 1.01—1.21, $p = 0.034$), 1.3 (95 % CI: 1.1—1.52, $p = 0.002$), and 1.13 (95%CI: 1.04—1.22, $p = 0.004$), respectively.

Sensitivity analyses

Among patients with APACHE II data, we analysed the primary outcome of 30-day mortality following ICU admission (Table S7 in the supplementary file). After adjusting for disease severity using the APACHE II score and incorporating a time-by-TB interaction term, the aHRs of 30-day post-ICU admission mortality were found to be 1.54 (1.02—2.34) with a *p*-value of 0.041 for NTM-LD compared to the control group, and 2.57 (1.68—3.92) with a p-value of <0.001 for TB versus control.

The second analysis utilized the 30-day mortality, counting from the date of ICU admission for patients diagnosed with TB/NTM-LD before ICU, and from the diagnosis date for those diagnosed after ICU admission. Cox regression analysis for 30-day mortality further revealed that both NTM-LD (aHR: 1.58 [1.16—2.17]) and TB (aHR: 1.48 [1.22—1.79]) were significant in the multivariable analysis.

Subgroup analysis

Subgroup analyses were carried out for two distinct time periods: from 2008 to 2015 and from 2016 to 2021. For the 30-day mortality post-ICU admission, the aHR for NTM-LD versus control were 1.38 (95 % CI, 0.89—2.12) in 2008—2015 and 1.58 (95 % CI, 0.98—2.55) in 2016—2021. Similarly, for TB versus control, the aHRs were 1.62 (95 % CI, 1.25—2.08) in 2008—2015 and 1.32 (95 % CI, 0.99—1.77) in 2016—2021. These subgroup analysis results display a trend consistent with the overall conclusions of our study, thereby reinforcing our findings across the different time periods.

Table 2 Univariate and multiple Cox regression for 30-day mortality.

Variables	Category and Increment	Univariate Cox Regression		Multiple Cox Regression	
		HR (95 % CI)	*p*-value	aHR (95 % CI)	*p*-value
Patient groups					
Control	reference	1		1	
NTM-LD	comparator	1.21 (0.88–1.66)	0.24	1.49 (1.06–2.05)	0.015
TB	comparator	1.21 (1.01–1.46)	0.04	2.33 (1.68–3.24)	<0.001
Interaction (TB*follow-up time)				0.97 (0.94–0.99)	0.002
Age, years	≥65 vs.<65	0.83 (0.74–0.93)	0.002	0.96 (0.85–1.08)	0.479
Sex	Male vs. Female	1.08 (0.96–1.22)	0.193		
BMI (kg/m2)					
Normal weight (18.5 ≤ BMI < 24)	reference	1		1	
Underweight (BMI < 18.5)	comparator	0.84 (0.71–0.99)	0.033	0.87 (0.74–1.03)	0.106
Overweight (24 ≤ BMI < 27)	comparator	1.08 (0.93–1.26)	0.307	1.21 (1.04–1.4)	0.015
Obesity (27 ≤ BMI)	comparator	1.06 (0.9–1.25)	0.529	1.27 (1.07–1.52)	0.007
Smoke status	Ever vs. Never	1.05 (0.94–1.19)	0.371		
Cavity lesion	Yes vs. No	1.17 (0.95–1.44)	0.139		
Underlying disease					
Sinusitis	Yes vs. No	1.04 (0.54–2.01)	0.896		
COPD	Yes vs. No	0.68 (0.58–0.8)	<0.001	0.76 (0.64–0.9)	0.001
Asthma	Yes vs. No	0.6 (0.43–0.83)	0.002	0.65 (0.47–0.9)	0.01
Bronchiectasis	Yes vs. No	0.88 (0.62–1.26)	0.487		
IPF	Yes vs. No	1.71 (1.39–2.11)	<0.001	1.76 (1.42–2.17)	<0.001
Heart failure	Yes vs. No	0.8 (0.69–0.92)	0.002	0.90 (0.78–1.05)	0.18
Diabetes mellitus	Yes vs. No	0.74 (0.65–0.83)	<0.001	0.75 (0.66–0.86)	<0.001
Kidney disease	Yes vs. No	1.25 (1.11–1.41)	<0.001	1.4 (1.24–1.6)	<0.001
ESKD	Yes vs. No	3.27 (2.35–4.56)	<0.001	3.13 (2.23–4.41)	<0.001
GERD	Yes vs. No	0.97 (0.78–1.21)	0.794		
Cirrhosis	Yes vs. No	1.4 (0.53–3.74)	0.498		
Active cancer	Yes vs. No	2.46 (2.19–2.75)	<0.001	2.59 (2.3–2.91)	<0.001
Autoimmune disease	Yes vs. No	1.51 (1.2–1.91)	0.001	1.53 (1.21–1.94)	0.001
Post transplant	Yes vs. No	1.1 (0.74–1.65)	0.636		
ICU diagnosis					
Pulmonary infections[a]	Yes vs. No	1.03 (0.91–1.16)	0.655		
Respiratory failure	Yes vs. No	1.27 (1.13–1.43)	<0.001	1.34 (1.19–1.52)	<0.001

[a] Pulmonary infection including pneumonia, lung abscess, or empyema NTM-LD. non-tuberculous mycobacterial lung disease.
NTM-LD non-tuberculous mycobacterial pulmonary disease, *TB* tuberculosis, *BMI* Body mass index, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *ESKD* end stage kidney disease, *GERD* gastroesophageal reflux disease.

Patients diagnosed with NTM-LD before or after ICU admission, the median durations were 18 days (Q1-Q3: 8–50) before ICU or 1 day (Q1-Q3: 0–3) after ICU, respectively. In the additional subgroup analysis focusing on patients diagnosed with NTM-LD after ICU admission, which constituted 51 % of our original cohort, we observed aHR of 1.19 (95 % CI, 0.73–1.92) for NTM-LD with a p-value of 0.43, and an aHR of 1.58 (95 % CI, 1.22–2.06) for TB with a p-value of <0.001 (Table S8 in the supplementary file).

Discussion

This study investigated the impact of NTM-LD on critically ill patients, with a focus on survival and utilization of mechanical ventilation, using a large cohort composed of 5996 patients who were admitted to the ICU. The cohort included 173 (2.9 %) patients diagnosed with NTM-LD and 541 (9.0 %) patients with TB. The overall 30-day mortality rate was 22.18 %, and the 30-day mortality rates for each group were higher in the NTM-LD group (26.01 %) and the TB group (25.69 %) than in the control group (21.7 %). In multivariate Cox regression, patients in the NTM-LD and TB groups had significantly higher aHR of 1.49 (95 % CI, 1.06–2.05, $p = 0.015$) and 2.33 (95 % CI, 1.68–3.24, $p < 0.001$) for 30-day ICU mortality, respectively, than the control group. In addition, patients with NTM-LD had significantly lower mechanical ventilation-free survival (aHR: 0.71 [95 % CI: 0.56–0.92], $p = 0.009$). Among NTM species, there was no significant difference in between-species impact on 30-day mortality and ventilator weaning. For 30-day mortality, patients with TB who were exposed to anti-mycobacterial agents before ICU admission experienced a greater benefit compared to those treated after admission or those who received no treatment.

Our study found that patients diagnosed with NTM-LD or TB exhibited higher 30-day mortality rates than did those without mycobacterial infection. This finding echoes only one previous study, which surveyed NTM-LD patients before the time frame of this study and reported a quite high ICU

Table 3 Univariate and multiple Cox regression for mechanical ventilation-free survival at 30 days in patients requiring invasive mechanical ventilation.

Variables	Category and Increment	Univariate Cox Regression		Multiple Cox Regression	
		HR (95 % CI)	*p*-value	aHR (95 % CI)	*p*-value
Patient groups					
Control	reference	1		1	
NTM-LD	comparator	0.78 (0.61−1)	0.050	0.71 (0.56−0.92)	0.009
TB	comparator	1.04 (0.9−1.19)	0.606	1.16 (0.92−1.46)	0.203
Interaction (TB*follow-up time)				0.98 (0.96−1.00)	0.045
Age, years	≥65 vs.<65	0.92 (0.85−1)	0.043	0.92 (0.84−0.99)	0.031
Sex	Male vs. Female	1.15 (1.06−1.24)	0.001	1.10 (1.01−1.21)	0.034
BMI (kg/m2)					
Normal weight (18.5 ≤ BMI < 24)	reference	1			
Underweight (BMI < 18.5)	comparator	1.07 (0.96−1.18)	0.218		
Overweight (24 ≤ BMI < 27)	comparator	1 (0.91−1.11)	0.976		
Obesity (27 ≤ BMI)	comparator	0.97 (0.87−1.09)	0.626		
Smoke status	Ever vs. Never	1.15 (1.06−1.24)	<0.001	1.08 (0.98−1.18)	0.108
Cavity lesion	Yes vs. No	0.93 (0.8−1.08)	0.344		
Underlying disease					
Sinusitis	Yes vs. No	1.62 (1.03−2.54)	0.036	1.44 (0.91−2.26)	0.116
COPD	Yes vs. No	1.12 (1.02−1.23)	0.016	1.06 (0.96−1.17)	0.278
Asthma	Yes vs. No	1.25 (1.07−1.47)	0.005	1.30 (1.1−1.52)	0.002
Bronchiectasis	Yes vs. No	1.25 (1−1.54)	0.045	1.24 (0.99−1.54)	0.058
IPF	Yes vs. No	0.78 (0.65−0.93)	0.007	0.75 (0.63−0.9)	0.002
Heart failure	Yes vs. No	1.01 (0.93−1.11)	0.763		
Diabetes mellitus	Yes vs. No	1.08 (1−1.17)	0.043	1.13 (1.04−1.22)	0.004
Kidney disease	Yes vs. No	0.8 (0.74−0.87)	<0.001	0.77 (0.71−0.84)	<0.001
ESKD	Yes vs. No	0.62 (0.38−1.01)	0.053		
GERD	Yes vs. No	1.09 (0.94−1.26)	0.262		
Cirrhosis	Yes vs. No	1.17 (0.56−2.45)	0.685		
Active cancer	Yes vs. No	0.84 (0.77−0.92)	<0.001	0.80 (0.74−0.88)	<0.001
Autoimmune disease	Yes vs. No	0.88 (0.73−1.07)	0.201		
Post transplant	Yes vs. No	0.88 (0.65−1.2)	0.416		
ICU diagnosis					
Pulmonary infections[a]	Yes vs. No	1.02 (0.95−1.1)	0.580		
Respiratory failure	Yes vs. No	0.75 (0.69−0.81)	<0.001	0.76 (0.7−0.82)	<0.001

[a] Pulmonary infection including pneumonia, lung abscess, or empyema.

NTM-LD non-tuberculous mycobacterial pulmonary disease, *TB* tuberculosis, *BMI* Body mass index, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *ESKD* end stage kidney disease, *GERD* gastroesophageal reflux disease.

mortality of 25.6 % (11/43).[14] Although the detailed relationship of ICU indication and NTM-LD could not be clarified in this database study, NTM-LD and the structural lung changes lead to poor outcomes when the patients are admitted to ICU. On the other hand, the high ICU mortality of TB patients is well documented, with reported pooled rates reaching up to 48 % and ranging from 21.6 % to 76.9 %, irrespective of the publication years of the studies.[17] This wide range of mortality may potentially be attributed to the alertness to TB and timing of treatment as well as differences in ICU admission policies and socioeconomic status. The similar high 30-day ICU mortality rates in both NTM-LD and TB patients might alert us not to ignore NTM-LD in ICU patients. However, determining the details of the impact of NTM-LD will require a large-scale prospective study for validation and investigation. Besides, the observed lack of mortality difference among various NTM species. It is indeed possible that this finding could be attributed to the small number of patients in each subgroup. This limitation in sample size may have impacted our ability to detect significant differences.

In addition, patients with NTM-LD were found to have poor mechanical ventilation-free status in the present study. This is important because a previous cohort study reported a higher risk of respiratory failure in NTM-LD patients, particularly in the first 6 months after diagnosis, than in the general population.[18] Furthermore, NTM outbreaks have been reported in various hospital settings, including ICU and long-term respiratory care units.[6,19,20] However, there is a paucity of studies examining the impact of NTM-LD on ventilator dependency following respiratory failure. Currently, there are no reports regarding NTM-LD and weaning from a mechanical ventilator except a small case series (N = 12), which reported successful liberation from mechanical ventilation in NTM patients who initiated anti-NTM treatment.[21] Our cohort, having a large case number (>100), might be more representative, and to our best knowledge, this is the first cohort study showing that NTM-

LD is correlated with poor outcome of ventilator weaning (weaning free rates: 54.62 % vs 64.59 % in the controls after 30 days). The impact of NTM-LD on ventilator weaning might need to be carefully interpreted and validated because of our retrospective study design, but we present this important real-world data, emphasizing that early diagnosis of NTM-LD is crucial for further ICU outcomes.

In the present study, overweight and obesity were associated with higher 30-day mortality, but it did not have a statistically significant effect on mechanical ventilation-free survival at 30 days, compared with normal body mass index (BMI) patients. BMI has long been used as a measure to estimate body fat, as it is calculated using only height and weight, as recommended by the World Health Organization (WHO). Excessive body fat is associated with an increased risk of mortality and morbidity due to chronic inflammation.[22] However, BMI is a limited indicator of body fat distribution and lean muscle mass, which are crucial factors in ICU patients.[23—25] Therefore, the overall impact of body fat on respiratory compliance, the interaction between adipose tissue and acute inflammation, and physiological reserve may vary among different study populations.[26] Further prospective studies are needed to investigate the role of other factors, such as body fat distribution and muscle mass, in relation to NTM-LD and ICU outcomes.

In the subgroup analysis evaluating patients with NTM-LD diagnosed either before or after ICU admission, we found median durations of 18 days (Q1-Q3: 8—50) and 1 day (Q1-Q3: 0—3) respectively, indicating that diagnoses often occurred close to ICU admission dates. Additionally, in a further subgroup analysis of patients diagnosed with NTM-LD post-ICU admission, representing 51 % of our initial cohort, the observed aHR was 1.19 (95 % CI, 0.73—1.92) for NTM-LD with a p-value of 0.43, and 1.58 (95 % CI, 1.22—2.06) for TB with a p-value of <0.001. While the aHR trend for NTM-LD paralleled our original analysis, the significance was diminished, likely due to a reduced number of cases. This also suggests that NTM-LD might be relatively indolent, with a shortened follow-up duration post-diagnosis (limited to within 30 days).

Because the study aim of ICU mortality is suggested to count since ICU admission,[27] we keep the 30-day mortality measurement since ICU admission for those diagnosed TB/NTM-LD before ICU. For those diagnosed with TB/NTM-LD after ICU admission, it's important to recognize that their indolent/subacute disease course may lead to infection and residence in the host for days or even months before NTM-LD is diagnosed. Furthermore, like NTM-LD patients who diagnosed after ICU admission, a median duration was only 1 day (Q1-Q3: 0—3) after ICU, which were closely to ICU admission date.

Our study has several limitations. First, due to a retrospective study design using a database, there was a potential of selection bias. The primary physicians often base their decision to test for NTM/TB without standard protocol. This approach could indeed influence the observed mortality rates, as it tends to identify patients with more severe underlying conditions or complications. Second, the patients of NTM-LD in the present database study were assessed by the microbiological diagnostic criteria. Although we presumed mycobacterial culture only in those patients with clinical symptoms or radiological suspicion for mycobacterial infection, the details of clinical and radiological findings could not be obtained in a database research and there is potential selection bias for enrolling NTM colonization as NTM-LD by only microbiological criteria. Although this approach differs from the comprehensive diagnostic strategy recommended in the guidelines, it is a common practice in NTM-LD database research,[28,29] and has a significant positive predictive value, estimated at around 86—90 %, in accurately identifying NTM-LD based on the microbiological standards set by the 2007 ATS guidelines.[1,30—33] Third, regarding model fit, our primary and secondary analysis indicated that the TB versus control comparison violated the proportional hazards assumption. Although we improved model fit by adding an interaction term between TB and follow-up time according to the literature,[16] further validation is required. Last, our study was conducted at multiple referral medical centres in Taiwan, which may have included patients with high severity and may limit the generalizability to other institutions or settings with different clinical practices and resources before validation. Nevertheless, as the largest study to date on the short-term survival of ICU patients with NTM-LD, our report highlights the urgent need for further research on this patient population across multiple settings.

In conclusion, our study findings highlight that both NTM-LD and TB contribute to increased 30-day mortality rates among patients in the ICU. Additionally, among patients with NTM-LD requiring mechanical ventilation, poorer outcomes were observed in terms of mechanical ventilation-free survival at 30 days. These results emphasize the significance of early detection and effective management of NTM-LD to enhance ICU outcomes, particularly in terms of reducing mortality and mitigating the risk of respiratory failure.

Author contributions

Y.-C. C. and C.-C. S. participated in the study conception and design, data acquisition, statistical analysis, data interpretation, and drafted the manuscript. C.-H. C. analysed and interpreted the data. C.-K. H., Y.-H. C., C.-J. L., C.-Y. C., and L.-C. K. contributed in data acquisition and interpretation. P.-H. W., J.-Y. W., S.-C. K., H.-C. W., and C.-J. Y. interpreted the data and prepared the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

This study was approved by the research ethics committee of National Taiwan University Hospital (201704001RINB). The need for obtaining informed consent was waived because the study used de-identified data.

Declaration of competing interest

All authors have reported that they have no financial or nonfinancial conflicts of interest related to this work.

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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.2023.12.009.