Original Article

Prognostic nutritional index as a predictor of mortality in nontuberculous mycobacterial lung disease

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Background: Although the association between nontuberculous mycobacterial lung disease (NTM-LD) and malnutrition is known, there are a few reports on the association between the nutritional score and death in patients with NTM-LD. This study investigated the association between the nutrition data at the time of NTM-LD diagnosis and death.

Methods: A retrospective study was conducted for patients with NTM-LD who visited the Maebashi Red Cross Hospital from January 2014 to December 2018. The patients were divided into the survival and death groups and analyzed statistically.

Results: The diagnostic criteria for NTM-LD were met by 150 patients. The median age was 70 years (range, 20–94 years). There were 51 (34.0%) men and 99 (66.0%) women. In the death group, the body mass index was significantly low, and there were significantly more patients with asthma. Further, computed tomography at the first visit revealed significantly fewer cases of the nodular bronchiectasis type. In the hematologic examination at the time of NTM-LD diagnosis, the white blood cell, neutrophil, and platelet counts and C-reactive protein and serum calcium levels were significantly higher in the death group, while the serum albumin level was significantly lower. In the death group, the prognostic nutritional index (PNI), calculated from the hematologic findings, was significantly lower, while the Glasgow Prognostic Score (GPS) was significantly higher. A logistic regression analysis was performed on items with significant differences, and the PNI and platelet count were independent factors predicting death.

Conclusions: PNI might be effective as a prognostic factor for NTM-LD.

Keywords: Glasgow Prognostic Score (GPS); mortality; nontuberculous mycobacterial lung disease (NTM-LD); nutrition; prognostic nutritional index (PNI)

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Introduction

The prevalence of nontuberculous mycobacterial lung disease (NTM-LD) is increasing every year (1). Malnutrition is often found in advanced NTM-LD (2). The prognostic nutritional index (PNI) and Glasgow Prognostic Score (GPS) are known as indicators related to nutrition. In tuberculosis, the serum albumin level and PNI score are associated with the cavitation (3). Moreover, the GPS, which is a prognostic indicator for malignant tumors, predicts the prognosis of idiopathic pulmonary fibrosis (4), but there are no reports on the association between these

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indicators and NTM-LD. We statistically analyzed the association between these indicators and the prognosis of NTM-LD.

Methods

Subjects

This was a single-center retrospective study. Among the patients who visited the Department of Respiratory Medicine at the Maebashi Red Cross Hospital from January 1, 2014, to December 31, 2018, those who were diagnosed according to the criteria of the American Thoracic Society/Infectious Disease Society of America from 2007 were enrolled (5). Patients lacking information, patients less than 20 old years, and patients who refused to enroll in the trial were excluded. Patients diagnosed with NTM were followed up until the last visit of the study period. This study disclosed information using an opt-out method and excluded patients who did not consent to the study. This study was reviewed and approved by the Maebashi Red Cross Hospital Ethics Committee on July 5, 2019 (acceptance no. 2019–15). The outcome of this study did not affect the future, and the personal data of the subject was strictly secured.

Clinical assessment

Statistical data (date, height, and weight at the time of NTM-LD diagnosis and sex), sociological data (underlying diseases, smoking history), hematologic data at the time of NTM-LD diagnosis, bacteriologic data, and imaging data were acquired. Body mass index (BMI), PNI [10 × serum albumin level (g/dL) + 0.005 × lymphocyte count (/μL)] (6), and GPS were calculated from the acquired data. The GPS was defined as 2 points, 1 point, and 0 point with elevated C-reactive protein (CRP) (>1 mg/dL) and hypoalbuminemia (<3.5 g/dL), elevated CRP (>1 mg/dL) or hypoalbuminemia (<3.5 g/dL), and neither elevated CRP nor hypoalbuminemia, respectively (7). We categorized the patients based on the onset of malignant tumors during the follow-up as follows: the none group, patients without tumor development; the past group, patients with a tumor diagnosed more than 1 month before the NTM-LD diagnosis; the concurrent group, patients with a tumor diagnosed within 1 month before or after the NTM-LD diagnosis; the future group, patients with a tumor diagnosed more than 1 month after the NTM-LD diagnosis. Also, we defined the death group as the patients who died during the follow-up.

Statistical analysis

Statistical analysis was performed using the software R version 3.4.1 and EZR version 1.37. Continuous variables were analyzed using the Mann-Whitney U test and expressed as the median (maximum and minimum). Nominal variables were analyzed using Fisher's exact test and expressed as the number and ratio. P value <0.05 was considered statistically significant.

A logistic regression analysis was performed for items with a significant difference, and the odds ratio and 95% confidence interval were calculated. A multivariate analysis was performed after adjusting for age and sex.

Statistical analysis limited to *Mycobacterium avium* complex (MAC) patients was performed similarly.

Results

Two hundred and fifteen patients visited our hospital as NTM in the study period, excluding 60 patients who did not meet the American Thoracic Society/Infectious Disease Society of America criteria and 5 patients who were diagnosed with non-NTM. We enrolled 150 patients with NTM-LD who visited our hospital from January 2014 to December 2018. The median follow-up time was 24 months (range, 0–230 months), and 17 patients died during the follow-up time. No patients died by NTM-LD. The presence of symptoms before the study period could not investigate because of the lack of information. The median age at the time of diagnosis was 70.0 years (range, 20–94 years). There were 51 men (34.0%) and 99 women (66.0%). No patients in this study were positive for the human immunodeficiency virus. Among the identified bacterial species, *M. avium*, *M. intracellulare*, and co-infection with *M. avium* and *M. intracellulare* accounted for 81 (54.0%), 51 (34.0%), and 6 (4.0%), respectively (*Figure 1*). In addition, *M. kansasii*, *M. xenopi*, *M. gordonae*, *M. terrae*, *M. szulgai*, *M. fortuitum*, and *M. abscessus* were identified. The bacterial species were unidentified in 16 cases because of the denaturation of the bacteria or the lack of the examination by DNA-DNA hybridization method. We divided the patients into the survival and death groups and analyzed the factors associated with death (*Table 1*). In the death group, patients were older at the time of diagnosis {79 [59–86] *vs.*

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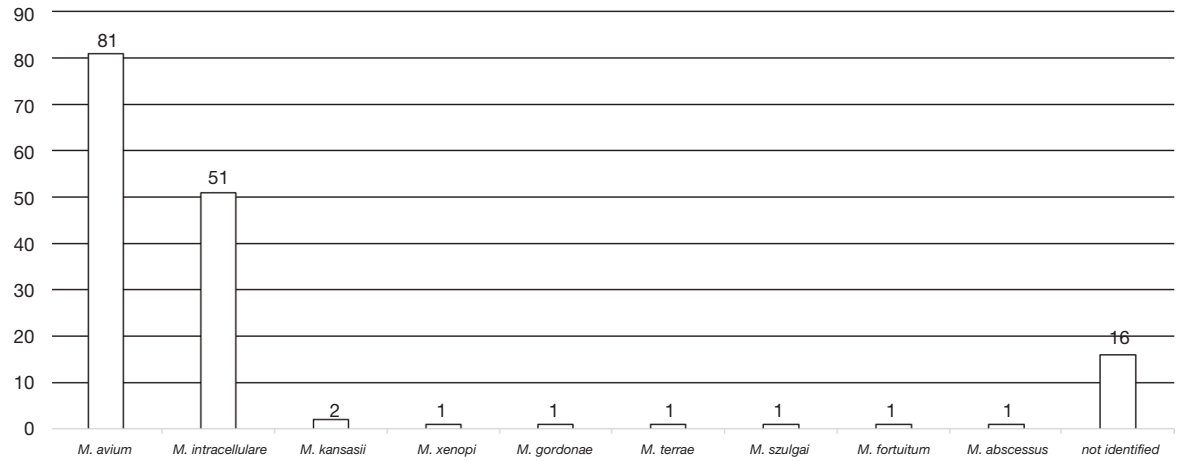

Figure 1 Cause bacteria species in nontuberculous mycobacterial lung disease.

70 [20–94] years; P=0.085}, and there was a higher proportion of male [9 (52.9) *vs.* 42 (31.6), P=0.103], but without a significant difference. BMI was significantly lower in the death group [15.50 (11.17–25.81) *vs.* 18.99 (12.56–31.61) (kg/m^2); P=0.002], and there were significantly more cases with asthma [4 (23.5) *vs.* 2 (1.5); P=0.002]. Computed tomography (CT) at the first visit showed significantly fewer cases of nodular bronchiectasis (NB) type in the death group [7 (41.2) *vs.* 93 (69.9); P=0.027]. There was no difference cavitation, the bacterial species or the degree of sputum smear between the survival and death groups. In addition, we analyzed the association between tumor complications and death before the diagnosis, at the time of diagnosis, and after the diagnosis but found no significant differences. Hematologic examination at the time of NTM-LD diagnosis revealed that the death group had significantly higher white blood cell count [7,550 (3,500–14,000) *vs.* 5,900 (3,000–14,400) (/μL); P=0.004], neutrophil count [5,687 (2,426–10,794) *vs.* 4,020 (1,408 *vs.* 12,052) (/μL); P<0.001), and platelet count [308.5 (106–486) *vs.* 230.0 (52–519) (×10^3/μL); P=0.018]. The serum albumin level was significantly lower in the death group [3.25 (2.60–4.20) *vs.* 4.00 (1.00–4.80) (g/dL); P<0.001), while the CRP level [1.20 (0.10–10.83) *vs.* 0.17 (0.1–19.21) (mg/dL); P=0.001] and calcium concentration [9.50 (9.00–10.40) *vs.* 9.30 (8.50–10.40) (mg/dL); P=0.033] were significantly higher. The anti-glycopeptidolipid core IgA antibody was higher in the survival group, although without statistical significance [1.99 (0.50–10.00) *vs.* 0.5 (0.5–10.0) (U/mL); P=0.125]. PNI was significantly lower in the death group [39.93 (29.85–51.41) *vs.* 47.56 (26.66–57.15); P<0.001], while GPS was significantly higher (P<0.001).

The logistic regression analysis was performed for the items with P<0.05 (BMI, presence of asthma, NB type on CT, white blood cell and platelet counts, calcium concentration, PNI, and GPS) (*Table 2*). The serum albumin and CRP levels and neutrophil count were excluded based on collinearity. In the multivariate analysis after adjusting for age and sex, the platelet count [odds ratio (OR): 1.090; 95% confidence interval (CI): 1.010–1.180; P=0.023] and PNI (OR: 0.871; 95% CI: 0.786–0.966; P=0.009) were the independent factors predicting prognosis.

We added the analysis against MAC (*Table 3*). Similar to all NTM species, we found significant differences in BMI, asthma, NB type in CT, WBC, Neutrophil count, Albumin, CRP, PNI, and GPS. In addition, significant differences were found in age, lymphocyte count, and cavitation, but no significant differences were found in serum calcium value and platelet count. Logistic regression analysis was performed for items with significant differences (*Table 4*). In a multivariate analysis corrected for age and sex, BMI and GPS were independent predictors of death.

Discussion

NTM-LD has a high mortality rate. Marras *et al.* reported mortality rates of 20.7 per 1,000 person-years and 5.6 per 1,000 person-years in the NTM-LD and control groups, respectively (8). In addition, pulmonary hypertension, pulmonary fibrosis, male sex, older age, and immunosuppressive therapy use are risk factors for high mortality in patients NTM-LD (9,10). Although there are a few reports on the association between malignant tumors and NTM-LD, lung cancer was present in 1.7–3.9% of

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Table 1 Comparison between survival group and death group in nontuberculous mycobacterial lung disease

Variable	Survival (n=133)	Death (n=17)	P value
Age	70 (20, 94)	79 (59, 86)	0.085
Male	42 (31.6)	9 (52.9)	0.103
Body mass index (kg/m^2)	18.99 (12.56, 31.61)	15.50 (11.17, 25.81)	0.002**
Follow-up (month)	24 (0, 230)	23 (0, 68)	0.370
Smoking	41 (31.8)	10 (58.8)	0.055
Underlying disease			
Asthma	2 (1.5)	4 (23.5)	0.002**
COPD	11 (8.3)	4 (23.5)	0.070
Diabetes mellitus	10 (7.5)	3 (17.6)	0.168
Interstitial lung disease	1 (0.8)	0 (0.0)	1.000
Tumor none	106 (80.3)	10 (58.8)	
Past	22 (16.7)	4 (23.5)	0.511
Concurrent	1 (0.8)	2 (11.8)	0.064
Future	3 (2.3)	1 (5.9)	0.385
Bacterial species			
M. avium	75 (56.4)	6 (35.3)	0.124
M. intracellulare	44 (33.1)	7 (41.2)	0.589
M. kansasii	1 (0.8)	1 (5.9)	0.214
Other species or not identifiable	18 (13.5)	4 (23.5)	0.279
Sputum smear at diagnosis			0.352
0/+/–/1+/2+/3+	62/6/20/26/19	6/0/2/3/6	
CT pattern			
NB type	93 (69.9)	7 (41.2)	0.027*
FC type	10 (7.5)	2 (11.8)	0.628
NB + FC type	23 (17.3)	5 (29.4)	0.317
Unclassified type	7 (5.3)	2 (11.8)	0.270
Cavitation	33 (24.8)	7 (41.2)	0.157
Laboratory data at diagnosis			
White blood cell count (/μL)	5,900 (3,000, 14,400)	7,550 (3,500, 14,000)	0.004**
Neutrophil count (/μL)	4,020 (1,408, 12,052)	5,687 (2,426, 10,794)	<0.001**
Lymphocyte count(/μL)	1,308 (558, 2,925)	1,024 (694, 2,156)	0.066
Platelet count (×10^3/μL)	230 (52, 519)	308.5 (106, 486)	0.018*
Albumin (g/dL)	4.00 (1.00, 4.80)	3.25 (2.60, 4.20)	<0.001**
Lactate dehydrogenase (IU/L)	191 (81, 714)	185 (117, 365)	0.961
C-reactive protein (mg/dL)	0.17 (0.10, 19.21)	1.20 (0.10, 10.83)	0.001**

Table 1 (*continued*)

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Table 1 (*continued*)

Variable	Survival (n=133)	Death (n=17)	P value
Calcium (mg/dL)	9.30 (8.50, 10.40)	9.50 (9.00, 10.40)	0.033*
Total cholesterol (mg/dL)	194 (83, 325)	189 (101, 266)	0.608
D-dimer (μg/mL)	1.10 (0.50, 49.30)	1.30 (1.10, 4.30)	0.579
Hemoglobin A1c (%)	5.80 (5.00, 10.00)	5.60 (4.90, 8.80)	0.635
Anti-GPL core IgA antibody (U/mL)	1.99 (0.50, 10.00)	0.50 (0.50, 10.00)	0.125
PNI	47.56 (26.66, 57.15)	39.93 (29.85, 51.41)	<0.001**
GPS 0	90 (72.6)	5 (31.3)	<0.001**
1	20 (16.1)	3 (18.8)	
2	14 (11.3)	8 (50.0)	

Values are median (minimum, maximum) or number (percentage). The nominal variables are analyzed Fisher's exact test and the continuous variables are analyzed by Mann-Whitney-U test. *, P<0.05; **, P<0.01. COPD, chronic obstructive pulmonary disease; NB, nodular bronchiectatic; FC, fibro cavitary; Anti-GPL core IgA antibody, anti-glycopeptidolipid core IgA antibody; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score.

Table 2 Logistic regression analysis about prognostic factors of patients with nontuberculous mycobacterial lung disease

Variable	Univariate	P value	Adjusted multivariate[a]	P value
Age	1.050 (0.993–1.100)	0.090	–	–
Male	2.440 (0.879–6.760)	0.087	–	–
Body mass index	0.758 (0.625–0.921)	0.005**	–	–
Asthma	20.20 (3.36–121.00)	0.001**	–	–
NB type in CT	0.301 (0.107–0.847)	0.023*	–	–
White blood cell count	1.000 (1.000–1.000)	0.011*	–	–
Platelet count	1.010 (1.000–1.010)	0.006**	1.090 (1.010–1.180)	0.023*
Calcium	6.610 (1.430–30.60)	0.016**	–	–
PNI	0.845 (0.769–0.929)	<0.001**	0.871 (0.786–0.966)	0.009**
GPS	3.210 (1.710–6.050)	<0.001**	–	–

Values are revealed the odds ratio and 95% confidence interval. [a], multivariate analysis was adjusted by age and sex; *, P<0.05; **, P<0.01. NB, nodular bronchiectatic; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score.

patients with NTM-LD (11,12).

In our knowledge, this is the first report that PNI was identified as an independent factor predicting death. The PNI score is calculated using the lymphocyte count and serum total cholesterol level (6). Initially, it was reported that low PNI scores were associated with the prognosis of gastrointestinal cancers after surgery. Additionally, recent reports stated that PNI predicted the development of cavitation in pulmonary tuberculosis (3) and was associated with one-year mortality in heart failure (13). Although it is unclear why PNI is associated with death in NTM-LD, it may be because the decline in nutritional and immunologic statuses is associated with the development and progression of secondary diseases in addition to the progression of NTM-LD. The sputum smear at the first visit or the NTM species were not associated with death, and the association between the NTM-LD disease status and death was not clear. The lymphocyte count and serum total cholesterol level in PNI were not significantly associated with death in this study, but it was reported that

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Table 3 Comparison between survival group and death group in *Mycobacterium avium* complex

Variable	Survival (n=114)	Death (n=12)	P value
Age	70 (20, 94)	80 (59, 86)	0.042*
Male	33 (28.9)	6 (50.0)	0.187
Body mass index (kg/m^2)	19.02 (12.69, 31.61)	15.10 (11.17, 21.95)	0.001**
Follow-up (month)	23.5 (0, 135)	26 (2, 52)	0.628
Smoking	33 (29.7)	6 (50.0)	0.193
Underlying disease			
Asthma	1 (0.9)	2 (16.7)	0.024*
COPD	8 (7.0)	1 (8.3)	1.000
Diabetes mellitus	10 (7.5)	3 (17.6)	0.168
Interstitial lung disease	1 (0.9)	0 (0.0)	1.000
Tumor none	93 (82.3)	7 (58.3)	
Past	17 (15.0)	4 (33.3)	0.221
Concurrent	1 (0.9)	0 (0.0)	1.000
Future	2 (1.8)	1 (8.3)	0.261
Bacterial species			
M. avium	75 (65.8)	6 (50.0)	0.346
M. intracellulare	44 (38.6)	7 (58.3)	0.223
Sputum smear at diagnosis			0.102
0/ +/–/1+/2+/3+	47/6/19/25/17	4/0/1/1/6	
CT pattern			
NB type	78 (68.4)	4 (33.3)	0.024*
FC type	7 (6.1)	2 (16.7)	0.205
NB + FC type	22 (19.3)	5 (41.7)	0.130
Unclassified type	7 (6.1)	1 (8.3)	0.562
Cavitation	29 (25.4)	7 (58.3)	0.038*
Laboratory data at diagnosis			
White blood cell count (/μL)	5,900 (3,200, 13,100)	7,100 (3,500, 14,000)	0.030*
Neutrophil count (/μL)	4,034 (1,465, 12,052)	5,511 (2,426, 10,794)	0.013*
Lymphocyte count (/μL)	1,315 (560, 2,370)	983 (731, 2,156)	0.033*
Platelet count (×10^3/μL)	233 (55, 519)	243 (177, 486)	0.093
Albumin (g/dL)	4.05 (1.00, 4.80)	3.20 (2.60, 4.00)	<0.001**
Lactate dehydrogenase (IU/L)	191 (99, 714)	184 (117, 323)	0.340
C-reactive protein (mg/dL)	0.16 (0.10, 19.21)	1.64 (0.10, 10.83)	0.001**
Calcium (mg/dL)	9.30 (8.60, 10.40)	9.55 (9.10, 10.10)	0.060
Total cholesterol (mg/dL)	195 (130, 325)	184 (101, 266)	0.431

Table 3 (*continued*)

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Table 3 (*continued*)

Variable	Survival (n=114)	Death (n=12)	P value
D-dimer (μg/mL)	0.90 (0.50, 49.30)	1.30 (1.10, 4.30)	0.346
HbA1c (%)	5.80 (5.00, 10.00)	5.50 (4.90, 8.80)	0.477
Anti-GPL core IgA antibody (U/mL)	2.30 (0.50, 10.00)	0.62 (0.50, 10.00)	0.258
PNI	47.59 (30.49, 57.15)	39.32 (29.85, 43.65)	<0.001**
GPS			
0	79 (73.8)	3 (27.3)	<0.001**
1	18 (16.8)	0 (0.0)	
2	10 (9.3)	8 (72.7)	

Values are median (minimum, maximum) or number (percentage). The nominal variables are analyzed Fisher's exact test and the continuous variables are analyzed by Mann-Whitney-U test. *, P<0.05; **, P<0.01. COPD, chronic obstructive pulmonary disease; NB, nodular bronchiectatic; FC, fibro cavitary; Anti-GPL core IgA antibody, anti-glycopeptidolipid core IgA antibody; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score.

Table 4 Logistic regression analysis about prognostic factors of patients with *Mycobacterium avium* complex

Variable	Univariate	P value	Adjusted multivariate	P value
Age	1.060 (0.997–1.130)	0.062	–	–
Male	2.450 (0.738–8.160)	0.143	–	–
Body mass index	0.666 (0.521–0.851)	0.001**	0.642 (1.456–0.904)	0.011*
Asthma	22.60 (1.88–272.00)	0.014*	–	–
NB type in CT	0.231 (0.065–0.816)	0.023*	–	–
Cavitation	4.100 (1.21–13.90)	0.024*	–	–
White blood cell	1.000 (1.000–1.000)	0.011*	–	–
PNI	0.783 (0.683–0.897)	0.003**	–	–
GPS	5.050 (2.200–11.60)	<0.001**	5.180 (2.030–13.20)	<0.001**

Values are revealed the odds ratio and 95% confidence interval. Multivariate analysis was adjusted by age and sex. *, P<0.05; **, P<0.01. NB, nodular bronchiectatic; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score.

low lymphocyte counts predicted three-year mortality in severe chronic obstructive pulmonary disease (14), and the absolute lymphocyte count was an independent predictor of long-term mortality in acute heart failure (15). It is also known that hypocholesterolemia is associated with the development of some cancers (16). Low lymphocyte counts and hypocholesterolemia are associated with death in other diseases, and their combination might predict the death.

We examined GPS as a measure of the nutritional status, but it was not an independent factor associated with death. GPS is calculated from the CRP and serum albumin levels and predicts the prognosis in non-small cell lung cancer (7). Cowman *et al.* divided NTM-LD into the cavitary, nodular, and bronchiectasis types and found that lower albumin and higher CRP levels were associated with poor prognosis of cavitary NTM-LD (17). It is unclear why GPS based on the CRP and serum albumin levels is not associated with mortality in NTM-LD. One possibility is that NTM-LD needs different cut-off values when scoring CRP and serum albumin levels; however, this hypothesis has not been proven. On the other hand, GPS was an independent factor predicting death in the MAC group. Previous papers have reported that BMI predicted death in MAC (18,19), and in this study, BMI predicted death in the MAC

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group, but not all NTM. Although some predicted factors in mortality reported in the past were consistent with our study, some factors were not. As well, the different result was found in all NTM species and the MAC group. The differences in these results are difficult to explain but one of the reasons may be for the small number of patients included in this study. It is difficult to guess with only this study, and additional research with an increased number of patients is needed.

This study suggested that high platelet count at the time of NTM diagnosis may predict the death. In tuberculosis, it has been reported that the platelet associated with increased disease activity, proinflammatory, and tissue destruction through platelet-associated mediators (20,21). Although the role of platelets in NTM are not known in detail, the platelets may be associated with inflammatory by a mechanism similar to tuberculosis.

There were more patients based on asthma in the death group. There are reports that the use of inhaled corticosteroid (ICS) is involved in the development of NTM-LD (22,23). We cannot discuss the relationship between ICS use and death because we have not investigated the treatment of asthma, but NTM-LD may require careful use of ICS.

There are several limitations to this study. First, this was a single-center retrospective study with small sample size. In this study, only 150 people were enrolled, and the power to perform various analyzes is limited. Although it has been reported that age and sex are associated with death in NTM (9,10), our study did not show a significant difference. The result of P=0.090 for age and P=0.087 for sex in the univariate logistic analysis was not significantly but tend to associate. Analysis of the MAC group provided similar results to previously reported predictors of mortality, and the analysis for NTM may also be reliable. The little number of the patient may be the reason for the lack of significant results, and the study that increased enrolled patients is considered necessary for further studies. Second, the follow-up duration was relatively short and might not have been sufficient to examine the association of the parameters with death. Third, the bacterial species was not identified in some cases because of the denaturation of the bacteria or lack of examination; therefore, the data might not be homogeneous in the background factors. Finally, the analysis was performed using hematologic data at the time of diagnosis and could not be performed after the diagnosis because of the short follow-up duration and the lack of homogenized data. There is a need to examine whether or not the platelet count or PNI after the diagnosis could predict the prognosis. Future prospective multi-center studies with more cases and a longer follow-up duration are required.

Conclusions

Our data indicated that the PNI and platelet count at the time of NTM-LD diagnosis might be associated with mortality. Prospective, large-scale, multi-center studies are warranted.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-803). Dr. Horie reports personal fees from Astra Zeneca, personal fees from Teijin Pharma, personal fees from Boehringer Ingelheim Japan, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study disclosed information using an opt-out method and excluded patients who did not consent to the study. This study was reviewed and approved by the Maebashi Red Cross Hospital Ethics Committee on July 5, 2019 (acceptance no. 2019–15).

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