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Original Article

Serum HMGB1 and CA19-9 are independently associated with pulmonary cavity formation in patients with non-tuberculous mycobacterial pulmonary disease

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Abstract: Objectives: This work aimed to investigate the changes in serum inflammatory factors (IFs) in patients with nontuberculous mycobacterial pulmonary disease (NTM-PD) and to analyze their correlation with the presence of lung cavities. Methods: A retrospective study was conducted on 80 NTM-PD patients and 80 non-active pulmonary tuberculosis (Non-ATB) controls. Clinical characteristics, NTM species distribution, and chest CT findings were analyzed. Serum levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), procalcitonin (PCT), interleukin-1 (IL-1), IL-6, IL-8, high mobility group box protein 1 (HMGB1), Cystatin C (Cys C), and carbohydrate antigen 19-9 (CA 19-9) were measured by ELISA. Correlations between IFs and cavitation were assessed using Spearman's test. Results: Cavitation on CT was present in 31.2% of NTM-PD patients. Compared to Non-ATB controls, NTM-PD patients showed significantly higher levels of CRP, TNF-α, IL-6, HMGB1, Cys C, and CA19-9 (all $P<0.05$). Among NTM-PD patients, those with cavitation had significantly higher CRP, IL-6, IL-8, HMGB1, Cys C, and CA19-9 than those without cavitation (all $P<0.05$). Spearman analysis showed that cavitation positively correlated with CRP (r=0.284, $P<0.05$), IL-6 (r=0.195), IL-8 (r=0.189), HMGB1 (r=0.328), Cys C (r=0.272), and CA19-9 (r=0.312) (all $P<0.05$). ROC analysis revealed that the combination of HMGB1, CA19-9, and CRP yielded an AUC of 0.789 (95% CI: 0.672-0.906), with 76.0% sensitivity and 78.2% specificity. Multivariate logistic regression identified elevated HMGB1 (OR=1.142, 95% CI: 1.043-1.250, $P=0.004$), elevated CA19-9 (OR=1.067, 95% CI: 1.018-1.118, $P=0.007$), and coexisting bronchiectasis (OR=2.681, 95% CI: 1.076-6.684, $P=0.034$) as independent risk factors for cavitation. Conclusions: Serum HMGB1 and CA19-9 were independently associated with lung cavitation in NTM-PD patients and, together with CRP, may serve as non-invasive biomarkers for disease severity.

Keywords: Nontuberculous mycobacteria, pulmonary disease, inflammatory factors, lung cavities, correlation

Introduction

Nontuberculous mycobacteria (NTM) are mycobacteria other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. NTM infections in human tissues or organs can cause varying degrees of pathology in affected tissues or organs [1]. NTM pulmonary disease (NTM-PD) is the most common, accounting for approximately 90% of NTM infections [2]. It is believed that factors such as environmental exposure, bacterial infection, and host factors contribute to the development of NTM-PD, with higher risks observed in individuals with immunodeficiency, undergoing immunosuppressive therapy, chemotherapy, or organ transplantation [3, 4]. The clinical and imaging features of NTM-PD often overlapped with those of pulmonary tuberculosis, leading to frequent misdiagnosis in the absence of etiological identification. Typical chest CT manifestations included multiple nodules, bronchiectasis, and pulmonary cavities. Pulmonary cavities, which form following necrosis of diseased lung tissue and the entry of air after bronchial drainage, serve as important markers of active and progressive lung disease [5]. The presence of cavities was associated with poorer treatment outcome, higher recurrence rate, and increased morbidity in patients with NTM-PD [6]. Therefore, early and accurate assessment of pulmonary cavities is crucial for risk stratification and treat-

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ment decision-making. Currently, the evaluation of NTM-PD activity and severity relies mainly on clinical symptoms, chest imaging, and microbiological examinations. However, these methods all have limitations. Clinical symptoms (such as chronic cough, sputum production, and hemoptysis) lacked specificity and significantly overlapped with those of pulmonary tuberculosis and other chronic lung diseases. Chest CT findings might lag behind disease progression, and inter-observer variability remains a concern. Microbiological culture is time-consuming (slow-growing mycobacteria often required several weeks), and its sensitivity was suboptimal in patients with low bacterial loads [7]. Therefore, there is an urgent need for convenient, reliable, and non-invasive peripheral blood biomarkers to reflect disease activity, predict the presence of pulmonary cavities, and guide clinical management.

In recent years, several serum biomarkers have been explored for the diagnosis and monitoring of NTM-PD. For example, Krebs von den Lungen-6 (KL-6) and carbohydrate antigen 125 (CA125) were reported to be associated with disease severity [8, 9]. However, studies that simultaneously and systematically evaluate multiple inflammatory factors and specifically investigate their relationship with pulmonary cavity formation remain scarce. Previous studies mostly focused on one or two biomarkers, often had relatively small sample sizes, and rarely employed multivariate analysis to identify independent predictors of cavities. Furthermore, the potential roles of high mobility group box protein 1 (HMGB1) and carbohydrate antigen 19-9 (CA19-9) in cavitation formation in NTM-PD have not been thoroughly explored.

To address the above research gaps, the present study retrospectively enrolled 80 patients with active NTM-PD and systematically analyzed their clinical manifestations, NTM species distribution, and chest CT characteristics. Nine serum inflammatory factors (C-reactive protein [CRP], tumor necrosis factor-α [TNF-α], procalcitonin [PCT], interleukin-1 [IL-1], interleukin-6 [IL-6], interleukin-8 [IL-8], HMGB1, cystatin C [Cys C], and CA19-9) were measured, and their associations with the presence of pulmonary cavities were evaluated. This study was one of the few analyses that explored simultaneously the relationship between nine inflammatory mediators and cavitation in NTM-PD. Through multivariate logistic regression analysis, HMGB1 and CA19-9 were identified for the first time as independent predictors of pulmonary cavity formation, and a combined HMGB1 + CA19-9 + CRP predictive model was further constructed, which demonstrated superior predictive performance. This study provides non-invasive hematological candidate biomarkers for clinical use, assists clinicians in assessing the severity of NTM-PD and screens patients at high risk of cavitation. Markers may be used to monitor treatment response, thereby compensating for the limitations of traditional imaging and microbiological evaluation. Markers also may enable the differential diagnosis and severity assessment of NTM-PD.

Materials and methods

Study design and patient selection

A retrospective study was implemented, including clinical data from 80 patients diagnosed with NTM-PD at Affiliated Wuxi Fifth Hospital of Jiangnan University between June 2022 and December 2023. Inclusion criteria were: (I) meeting the diagnostic criteria for NTM-PD in the *Diagnosis and Treatment Guidelines for Nontuberculous Mycobacterial Diseases (2020 Edition)*; (II) confirmed diagnosis of NTM-PD through methods such as selective nitrate agar culture and bronchoscopy; (III) disease in the active phase; (IV) age ≥18 years; (v) initial diagnosis of NTM-PD with no prior anti-NTM treatment before enrollment.

Exclusion criteria were: (I) incomplete clinical data; (II) absence of chest CT imaging before treatment; (III) absence of laboratory tests before treatment; (IV) patients with active pulmonary tuberculosis; (V) patients with malignant tumors; (VI) patients with severe liver or kidney dysfunction; (vii) pregnant or lactating women. The inclusion and exclusion criteria were established in accordance with the "ATS/ERS/ESCMID/IDSA Official Clinical Practice Guidelines for the Treatment of Non-tuberculous Mycobacterial Pulmonary Disease" and similar published studies [10].

The patient screening flow chart is shown in **Figure 1**.

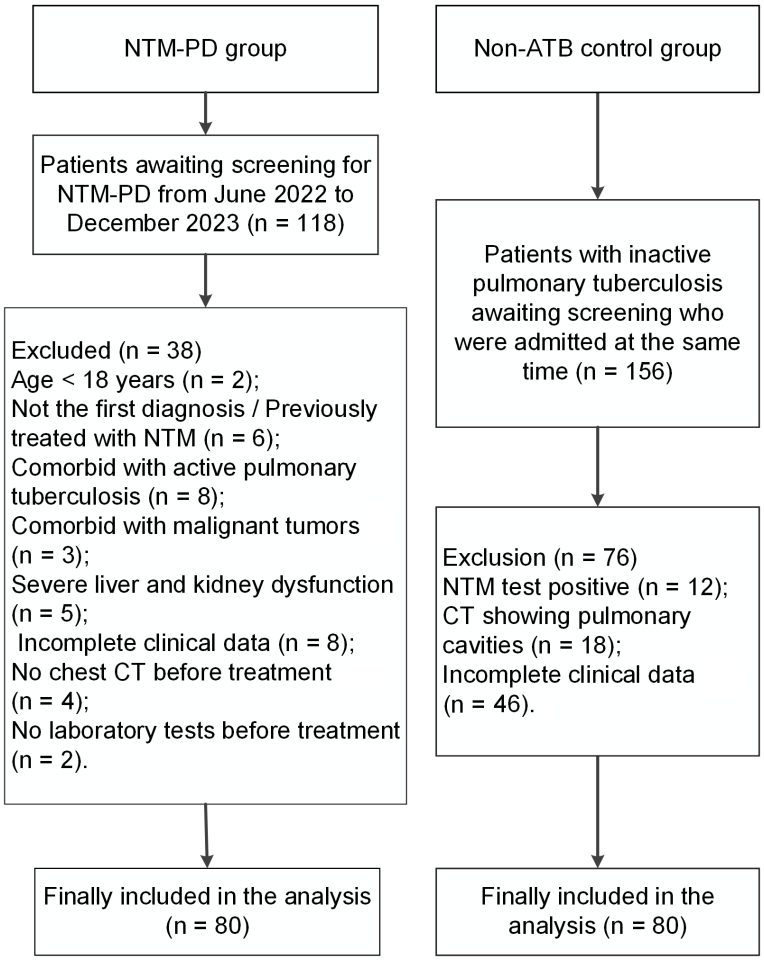

Figure 1. Patient screening flow chart.

Additionally, 80 patients diagnosed and treated for non-active pulmonary tuberculosis (Non-ATB) during the same period were recruited as controls, with complete clinical data, negative NTM tests, and no lung cavities observed on CT imaging. Of the 80 NTM-PD patients, there were 57 males and 23 females, aged 30 to 75 years, averaging (63.1 ± 8.6) years. Of the 80 Non-ATB patients, there were 50 males and 30 females, aged 30 to 72 years, averaging (59.2 ± 10.1) years. The general characteristics exhibited no significant differences between NTM-PD and Non-ATB patients. This study was approved by the Ethics Committee of Affiliated Wuxi Fifth Hospital of Jiangnan University.

Data extraction

All of the following data were independently extracted from the electronic medical record system by two researchers, and cross-checking was performed. In the event of any disagreement, a consensus was reached through discussion with a third researcher. The extracted data included: (1) Demographic and baseline information: age, sex, body mass index (BMI), smoking history, alcohol consumption history, and comorbidities (such as hypertension, diabetes mellitus, chronic liver disease); (2) Clinical manifestations including cough/sputum production, fever, hemoptysis, chest pain, chest tightness, wheezing; (3) Laboratory findings: levels of peripheral blood inflammatory factors (CRP, TNF-α, PCT, IL-1, IL-6, IL-8, HMGB1, Cys C, and CA19-9) measured in the early morning under fasting conditions before treatment; (4) Etiological data: results of mycobacterial culture and species identification; (5) Imaging data: findings from chest CT scans (features such as nodules, bronchiectasis, cavities, etc.). After data collection, all entries were logically verified by a second individual to ensure completeness and accuracy. The results of the baseline comparisons are presented in **Table 1**.

Outcome measures

All laboratory values were measured after hospital admission but before the initiation of anti-NTM treatment (at baseline). The primary outcome measure was the correlation between the occurrence of pulmonary cavities (presence/absence of cavities, as well as solitary/multiple cavities) in patients with NTM-PD and serum levels of inflammatory factors. Secondary outcome measures included: (1) Differences in serum inflammatory factor levels between the NTM-PD group and the Non-ATB group; (2) Differences in inflammatory factor levels between NTM-PD patients with cavities and those without cavities; (3) The predictive value of each inflammatory factor for pulmonary cavities.

Table 1. Comparison of baseline characteristics between the NTM-PD group and the non-ATB control group

Variable	NTM-PD group (n=80)	Non-ATB group (n=80)	Statistical value	*P* value
Age (years), median (IQR)	64.0 (55.0-71.0)	60.0 (50.5-69.0)	Z=-1.452	0.146
Sex [n (%)]			χ^2=1.425	0.233
Male	57 (71.3)	50 (62.5)		
Female	23 (28.7)	30 (37.5)		
Body mass index (BMI kg/m^2), mean ± SD	22.5 ± 3.2	23.1 ± 3.5	t=1.132	0.259
Smoking history [n (%)]	35 (43.8)	30 (37.5)	χ^2=0.651	0.420
Alcohol consumption history [n (%)]	20 (25.0)	18 (22.5)	χ^2=0.138	0.710
Comorbidities [n (%)]				
Hypertension	3 (3.8)	5 (6.3)	-	0.469*
Diabetes mellitus	5 (6.3)	6 (7.5)	χ^2=0.097	0.755
Chronic liver disease	2 (2.5)	1 (1.3)	-	>0.999*

Note: *Fisher's exact test was used. Abbreviations: NTM-PD, Nontuberculous Mycobacteria-Pulmonary Disease; Non-ATB, Non-Antituberculosis; IQR, interquartile range; SD, standard deviation; BMI, body mass index. Age was expressed as median (interquartile range), and the Mann-Whitney U test was used for comparison between groups. BMI was a normally distributed continuous variable, expressed as mean ± SD, and the independent samples t-test was used for comparison between groups. Categorical variables were expressed as number of cases (percentage), and the chi-square test or Fisher's exact test was used for comparison between groups.

Experimental methods

Isolation and identification of pathogens: The isolation and identification of mycobacteria in NTM-PD patients were conducted following the operational standards outlined in the Diagnostic and Bacteriological Examination Procedures for Tuberculosis. Mycobacteria were cultured using an automated mycobacterial culture detection system and drug susceptibility testing system. Preliminary identification of *Mycobacterium tuberculosis* complex and NTM was performed using a tuberculosis branched-chain antigen detection kit (colloidal gold method) purchased from Hangzhou Innovation Biotechnology Co., Ltd. The VITEK® MS mass spectrometry detection system (Shanghai Mérieux Diagnostic Products Co., Ltd.) was used for species identification of NTM. For sample preparation, a colony of 1 μL was inoculated into a centrifuge tube with 500 μL of 70% alcohol, along with a 0.5 mm glass beads. The mixture was shaken at 25°C for 5 minutes and left for 10 minutes. Following centrifugation at 12,000 rpm for 3 minutes, the supernatant was removed, and 10 μL of 70% formic acid (CH_2O_3) was applied and mixed. Subsequently, 1 μL of the supernatant was applied and dried for matrix application (VITEK® MS-CHCA matrix for use with VITEK® MS), followed by drying and machine detection. Based on the growth rate of NTM, they were categorized as rapidly growing mycobacteria (RGM) and slowly growing mycobacteria (SGM).

CT examination: NTM-PD patients underwent chest CT imaging using a Philips 64-slice spiral CT scanner. The CT examination parameters were set as follows: tube voltage of 120 kV, tube current of 150 mAs, rotation time of 0.5 s/r, pitch of 0.75, field of view of 320 mm, and slice thickness and interval of 5 mm. Before the examination, patients were instructed to breathe calmly and hold their breath during scanning from the lung apices to the costophrenic angle with relaxed breathing. After reconstruction, the slice thickness and interval were reduced to 1 mm. The reconstructed images were observed employing a dedicated image processing workstation with specific window settings: lung window (window level from -700 HU to -400 HU, window width from 1,000 HU to 1,500 HU) and mediastinal window (window level 30-60 HU, window width 300-500 HU).

Serological factor detection: Peripheral venous blood (5 mL) was collected from NTM-PD and Non-ATB patients in the early morning fasting state, treated with heparin sodium for anticoagulation, and then centrifuged at 3,000 rpm for 10 minutes to collect supernatant. Enzyme-linked immunosorbent assay (ELISA) was em-

ployed to measure the IFs, including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), procalcitonin (PCT), interleukin (IL)-1, IL-6, IL-8, high mobility group box protein 1 (HMGB1), Cystatin C (Cys C), and carbohydrate antigen 19-9 (CA 19-9) in the serum. ELISA kits were purchased from Thermo Fisher Scientific, China. A suitable volume of serum sample was added to the bottom of the ELISA plate and mixed well. After sealing, the plate was incubated at 37°C for 30 minutes, followed by removal of the serum from the wells and air-drying. The plate was washed with washing solution for 3 minutes, repeated 5 times. Then, 100 μL of chromogenic working solution was applied and mixed, and the plate was incubated at 37°C in the dark for 10 minutes. Eventually, the stop solution was applied, and absorbance was measured at 450 nm. The experiment was repeated thrice to calculate the average value.

Statistical analysis

Statistical analyses were performed using IBM SPSS 23.0 software. Continuous variables were tested for normality. Data following a normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between two groups were conducted using the independent samples t-test. Data with a skewed distribution were presented as median (interquartile range) [M (Q1, Q3)], and comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were expressed as counts (percentages) [n (%)], and group comparisons were made using the Chi-square test or Fisher's exact test.

Comparisons of clinical baseline characteristics and serum inflammatory factor levels between the NTM-PD group and the non-ATB group were performed using the methods described above. Spearman's rank correlation analysis was used to evaluate the correlations between serum inflammatory factor levels and the presence of pulmonary cavities. To assess the predictive value of serum inflammatory factors for pulmonary cavities, receiver operating characteristic (ROC) curves were plotted the area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated. Binary logistic regression analysis was conducted to identify independent factors associated with pulmonary cavity formation. Variables with $P<0.10$ by univariate analysis, along with clinically relevant factors (including age, sex, and the presence of bronchiectasis), were entered into the multivariate logistic regression model using the Forward LR (Likelihood Ratio) method. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each variable. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF), with VIF<5 considered acceptable. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test. All tests were two-sided, and $P<0.05$, was considered significant. Statistical symbols ($P<0.05$) in the figures are explained in figure legends.

Results

Comparison of clinical baseline data between the two patient groups

No significant differences were observed between the NTM-PD group and the non-ATB control group in terms of sex distribution, age, body mass index (BMI), or underlying diseases (diabetes mellitus, hypertension, etc.) (all $P>0.05$), indicating that the two groups were clinically comparable. Detailed data are presented in **Table 1**.

Clinical characteristics analysis

First, clinical manifestations were analyzed in 80 NTM-PD patients included in this study (**Figure 2A**). It was found that among the 80 NTM-PD patients, 4 were asymptomatic, while 76 presented with respiratory and/or systemic symptoms. Specifically, cough/expectoration was observed in 61 cases (76.3%), fever in 23 cases (28.8%), hemoptysis in 21 cases (26.3%), chest pain in 8 cases (10.0%), chest distress in 8 cases (10.0%), and panting in 4 cases (5.0%). Subsequently, comorbidities were analyzed among NTM-PD patients (**Figure 2B**). Among the 80 NTM-PD patients, 1 had no underlying diseases, while the remaining 79 patients had comorbidities. Specifically, bronchiectasis was present in 47 cases (58.8%), chronic obstructive pulmonary disease (COPD) in 13 cases (16.3%), chronic pulmonary fibrosis (CPF) in 9 cases (11.3%), pneumoconiosis in 2 cases (2.5%), diabetes in 5 cases (6.3%), and hypertension in 3 cases (3.8%).

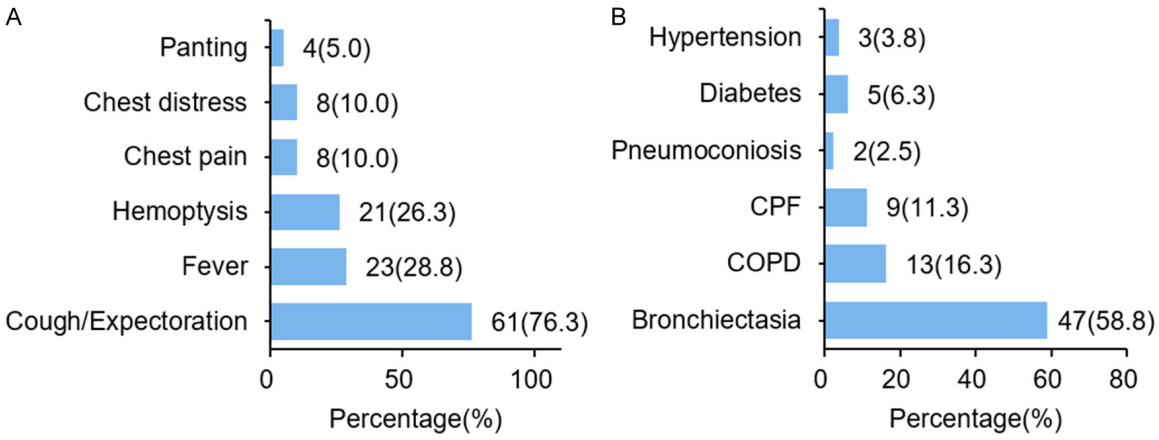

Figure 2. Clinical data analysis of NTM-PD patients. (A) The image represents clinical presentation data, (B) The image represents basic disease data.

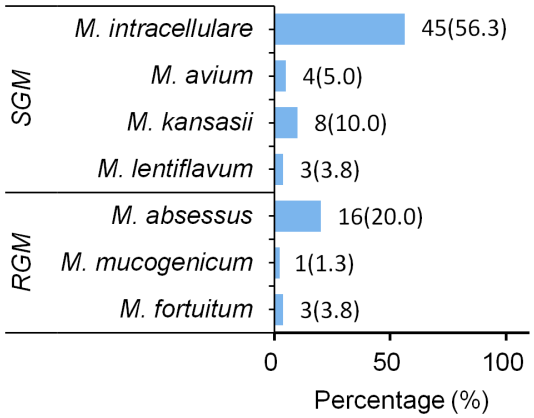

Figure 3. Characteristics of NTM bacterial strains in NTM-PD patients. M. fortuitum is Mycobacterium fortuitum; M. mucogenicum is Mycobacterium mucogenicum; M. abscessus is Mycobacterium abscessus; M. lentiflavum is Mycobacterium lentiflavum; M. kansasii is Mycobacterium kansasii; M. avium is Mycobacterium avium; M. intracellulare is Mycobacterium intracellulare.

Analysis of NTM bacterial strains in NTM-PD patients

In the analysis of NTM species distribution characteristics among 80 NTM-PD patients (**Figure 3**), it was found that the NTM positivity rate was 100.0%. Among these, RGM species included *M. fortuitum* in 3 cases (3.8%), *M. mucogenicum* in 1 case (1.3%), and *M. abscessus* in 16 cases (20.0%). SGM species included *M. lentiflavum* in 3 cases (3.8%), *M. kansasii* in 8 cases (10.0%), *M. avium* in 4 cases (5.0%), and *M. intracellulare* in 45 cases (56.3%).

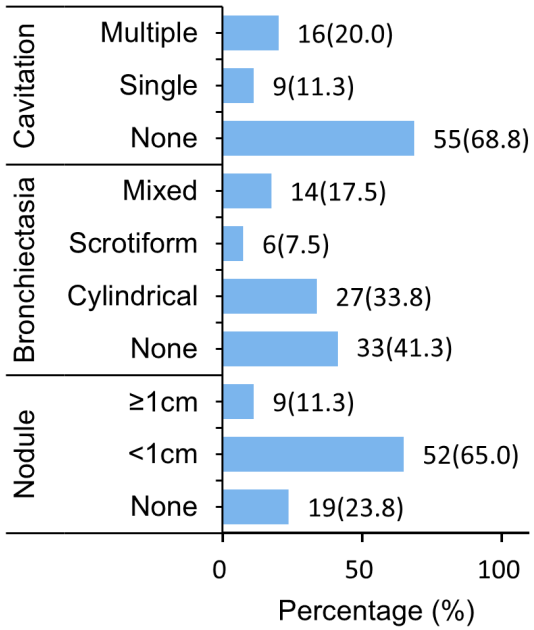

Figure 4. CT features of NTM-PD patients.

Analysis of CT manifestations in NTM-PD patients

CT imaging features were analyzed in 80 NTM-PD patients (**Figure 4**). Among these patients, 19 cases (23.8%) had no central nodules, 33 cases (41.3%) had no bronchiectasis, and 55 cases (68.8%) had no cavitation. Further analysis revealed the following distribution: Nodules <1 cm were present in 52 cases (65.0%) and ≥1 cm in 9 cases (11.3%). Among cases with bronchiectasis, the cylindrical type was found in 27 cases (33.8%), the saccular type in 6

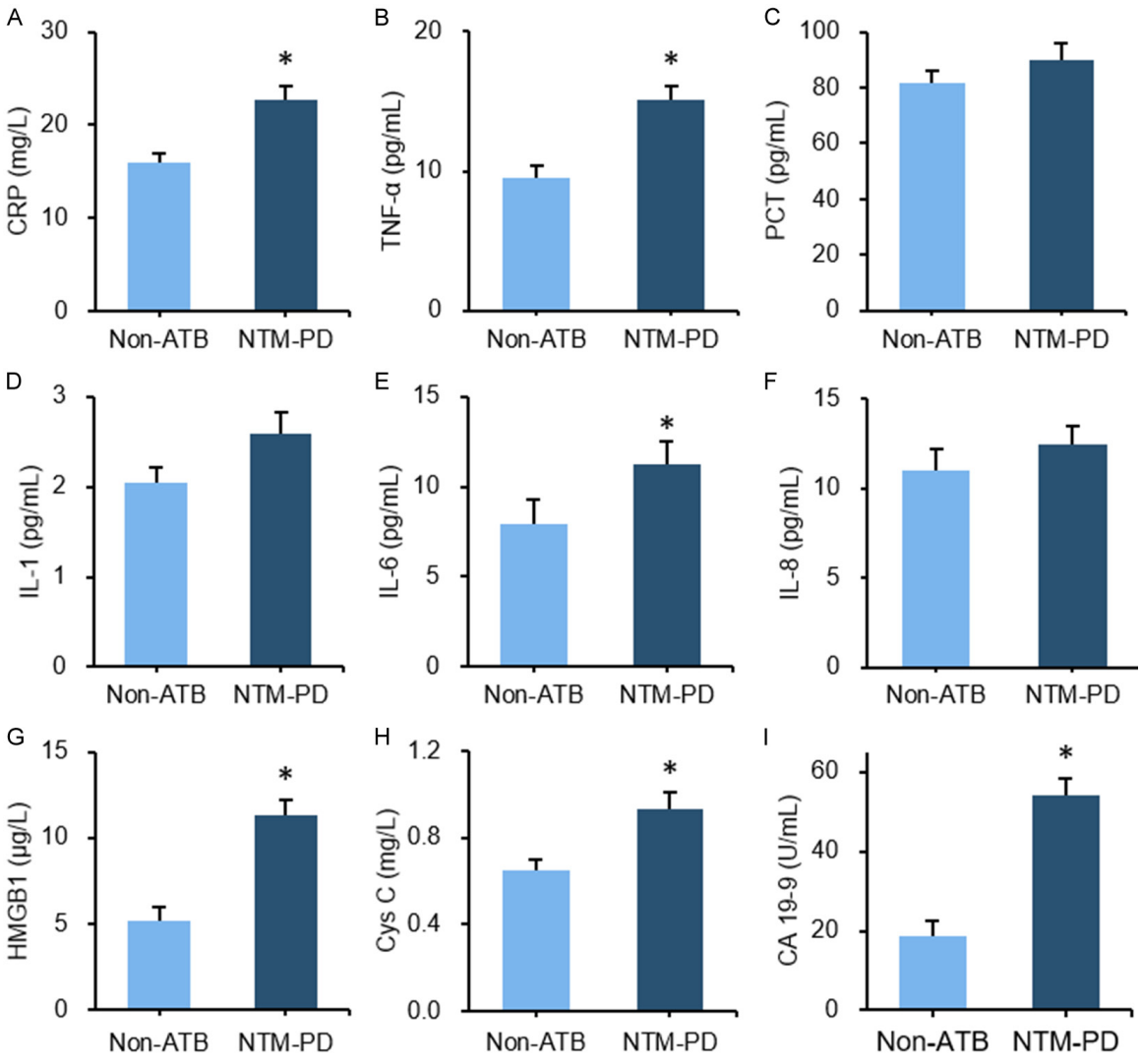

Figure 5. Comparison of serum inflammatory cytokine levels between NTM-PD and Non-ATB patients. A-I. These images represent CRP, TNF-α, PCT, IL-1, IL-6, IL-8, HMGB1, Cys C, and CA 19-9, respectively. *P<0.05 vs. Non-ATB group.

cases (7.5%), and a mixed type in 14 cases (17.5%). Regarding cavitation, single cavitations were seen in 9 cases (11.3%) and multiple cavitations in 16 cases (20.0%).

Serological factor levels in patients with NTM-PD and non-ATB

Serum levels of inflammation-related factors (CRP, TNF-α, PCT, IL-1, IL-6, IL-8, HMGB1, Cys C, and CA 19-9) were compared between NTM-PD patients and non-ATB patients. In **Figure 5A**, CRP levels in NTM-PD patients were significantly higher than those in non-ATB patients (P<0.05). In **Figure 5B**, TNF-α levels in NTM-PD patients were significantly elevated compared to non-ATB patients (P<0.05). **Figure 5C** shows no significant difference in PCT levels between NTM-PD and non-ATB patients (P>0.05). Similarly, **Figure 5D** reveals no significant difference in IL-1 levels between NTM-PD and non-ATB patients (P>0.05). In **Figure 5E**, IL-6 levels in NTM-PD patients were significantly higher than in non-ATB patients (P<0.05). **Figure 5F** indicates no significant difference in IL-8 levels between NTM-PD and non-ATB patients (P>0.05). **Figure 5G** shows significantly elevated HMGB1 levels in NTM-PD patients compared to non-ATB patients (P<0.05). In **Figure 5H**, Cys C levels were significantly higher in NTM-PD patients than in non-ATB patients (P<0.05). Finally, **Figure 5I** demonstrates that

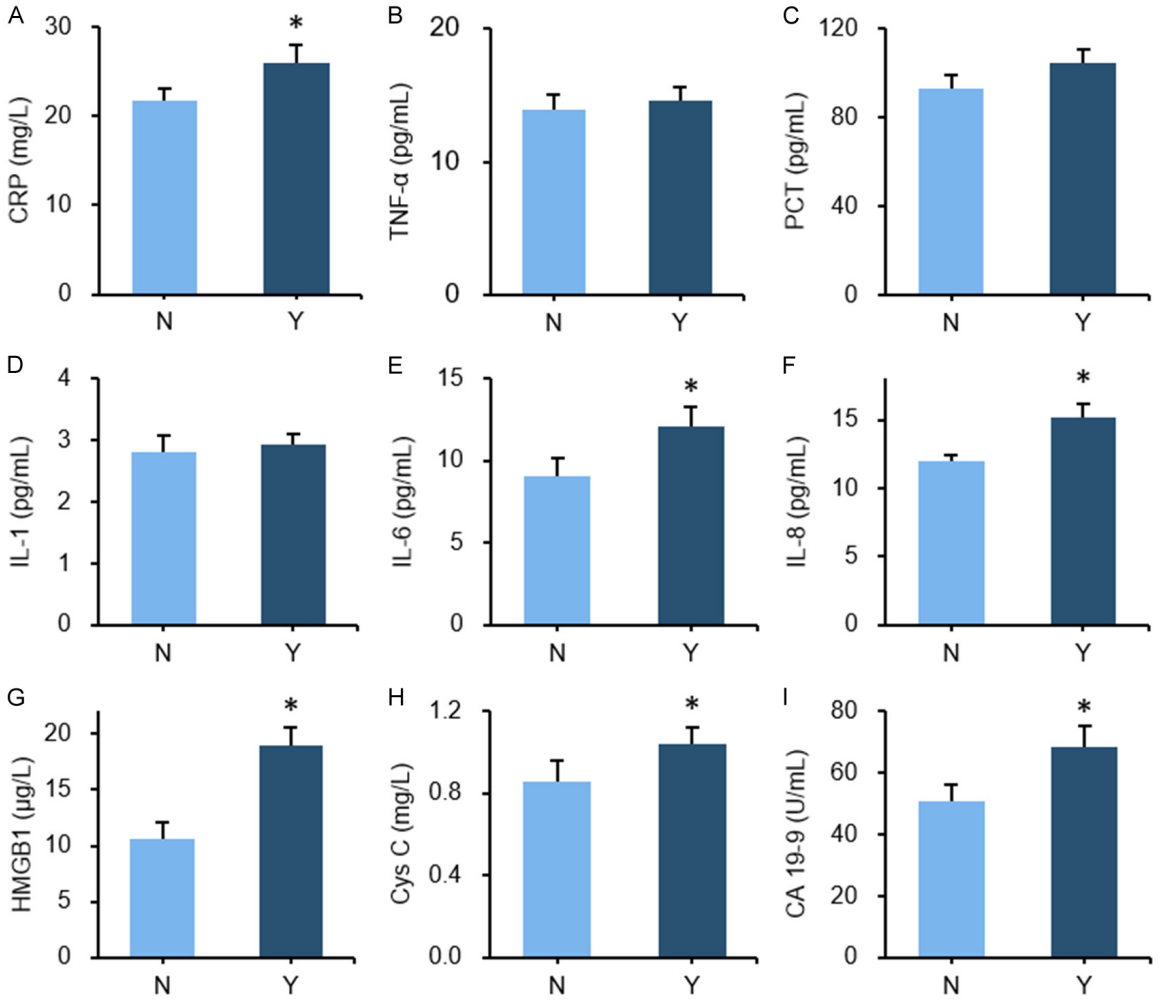

Figure 6. Comparison of serum IF levels between NTM-PD patients with and without cavitation. A-I. These images represent CRP, TNF-α, PCT, IL-1, IL-6, IL-8, HMGB1, Cys C, and CA 19-9, respectively. N indicates patients without cavitation, and Y indicates patients with cavitation. *P<0.05 vs. N group.

CA 19-9 levels in NTM-PD patients were significantly greater than in non-ATB patients (P<0.05).

Correlation analysis between serum factor levels and cavitation in NTM-PD patients

Serum levels of inflammation-related factors (CRP, TNF-α, PCT, IL-1, IL-6, IL-8, HMGB1, Cys C, and CA 19-9) were compared between NTM-PD patients with and without cavitation (**Figure 6**). In **Figure 6A**, CRP levels in patients with cavitation were significantly higher than in patients without cavitation (P<0.05). **Figure 6B** shows no significant difference in TNF-α levels between patients with and without cavitation (P>0.05). Similarly, **Figure 6C** reveals no significant difference in PCT levels between these groups (P>0.05). **Figure 6D** indicates no significant difference in IL-1 levels between patients with and without cavitation (P>0.05). In **Figure 6E**, IL-6 levels were significantly elevated in patients with cavitation compared to those without (P<0.05). **Figure 6F** demonstrates significantly higher IL-8 levels in patients with cavitation than in those without (P<0.05). HMGB1 levels were also significantly higher in patients with cavitation (**Figure 6G**) (P<0.05). **Figure 6H** indicates significantly higher Cys C levels in patients with cavitation compared to those without (P<0.05). Finally, **Figure 6I** shows that CA 19-9 levels were significantly greater in patients with cavitation than in those without (P<0.05).

A correlation analysis of serum IF levels in NTM-PD patients with cavitation (**Figure 7**) revealed notable associations. CRP showed positive cor-

	CRP	IL-6	IL-8	HMGB1	Cys C	CA 19-9	Cavitation
CRP	1						
IL-6	0.489	1					
IL-8	0.113	0.407	1				
HMGB1	0.255	0.518	0.420	1			
Cys C	0.082	0.257	0.312	0.042	1		
CA 19-9	0.036	0.106	0.055	0.214	0.031	1	
Cavitation	0.284	0.195	0.189	0.328	0.272	0.312	1

Figure 7. Spearman's correlation of serum IFs and cavity characteristics in NTM-PD patients.

relations with IL-6, HMGB1, and cavitation (r=0.489, 0.255, and 0.284, respectively; $P<0.05$). IL-6 exhibited positive correlations with IL-8, HMGB1, Cys C, and cavitation (r=0.407, 0.518, 0.257, and 0.195, respectively; $P<0.05$). IL-8 demonstrated positive correlations with HMGB1, Cys C, and cavitation (r=0.420, 0.312, and 0.189, respectively; $P<0.05$). HMGB1 showed positive correlations with CA 19-9 and cavitation (r=0.214 and 0.328, respectively; $P<0.05$). Cys C exhibited a positive correlation with cavitation (r=0.272, $P<0.05$). Additionally, CA 19-9 showed a positive correlation with cavitation (r=0.312, $P<0.05$).

Predictive value of serum inflammatory factors for NTM-PD cavities

Using CT-confirmed cavities as the gold standard, ROC curve analyses were performed for the six indicators that showed significant differences. The ROC curve results shown in **Figure 8** demonstrated that the AUC for HMGB1 was 0.712 (95% CI: 0.589-0.834), with an optimal cut-off value of 15.3 ng/mL, a sensitivity of 72.0%, and a specificity of 69.1%. The AUC for CA19-9 was 0.725 (95% CI: 0.602-0.847), with an optimal cut-off value of 24.8 U/mL, a sensitivity of 68.0%, and a specificity of 76.4%. The AUC for CRP was 0.689 (95% CI: 0.563-0.815), with an optimal cut-off value of 12.5 mg/L, a sensitivity of 80.0%, and a specificity of 58.2%. The AUC for Cys C was 0.704 (95% CI: 0.578-0.830), with an optimal cut-off value of 1.25 mg/L, a sensitivity of 64.0%, and a specificity of 74.5%. The AUCs for IL-6 and IL-8 were 0.668 and 0.652, respectively, indicating relatively lower predictive performance. Combined indicator analysis showed that the combination of HMGB1 + CA19-9 + CRP achieved an AUC of 0.789, with a sensitivity of 76.0% and a specificity of 78.2%, which was superior to any single indicator.

Multivariate regression analysis

Using CT-confirmed lung cavity (present/absent) as the dependent variable, variables with $P<0.10$ by univariate analysis (serum CRP, IL-6, IL-8, HMGB1, Cys C, CA19-9) together with

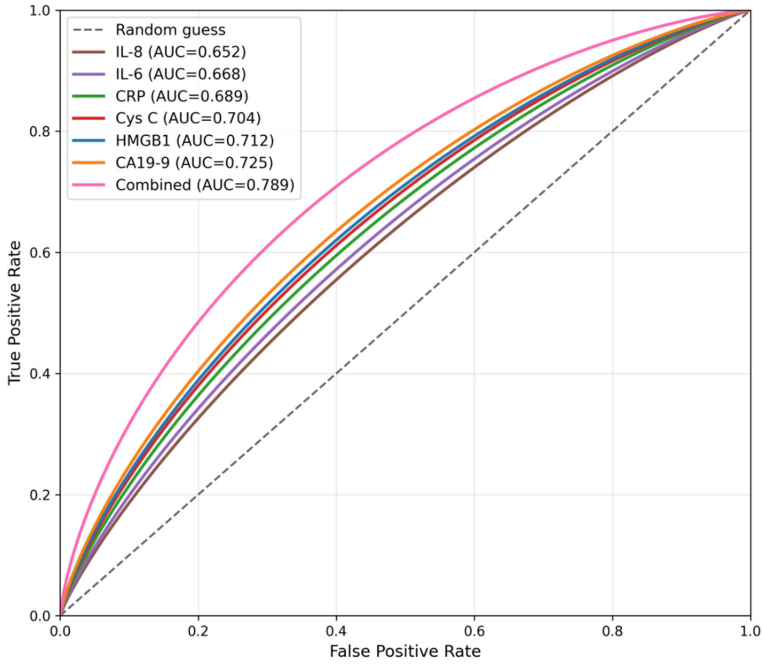

Figure 8. ROC curve.

clinically relevant factors (age, sex, and concurrent bronchiectasis) were entered into a multivariate logistic regression model. Variable selection was performed using the Forward LR (likelihood ratio) method. The full regression results are presented in **Table 2**. Among all variables included in the model, elevated serum HMGB1 (OR=1.142, 95% CI: 1.043-1.250, *P*=0.004), elevated CA19-9 (OR=1.067, 95% CI: 1.018-1.118, *P*=0.007), and the presence of concurrent bronchiectasis (OR=2.681, 95% CI: 1.076-6.684, P=0.034) were identified as independent risk factors for lung cavity formation. Serum CRP, IL-6, IL-8, Cys C, age, and sex were not independently associated with cavity formation (all *P*>0.05). The Hosmer-Lemeshow test indicated good model fit (χ^2=5.821, df=8, *P*=0.667), and no significant multicollinearity was detected among the independent variables (all VIF<3).

Discussion

In recent years, the incidence of NTM-PD has increased annually. Its clinical manifestations are similar to those of pulmonary tuberculosis, and misdiagnosis often occurs due to the lack of etiological identification [11]. The present study found that slow-growing mycobacteria predominated among patients with NTM-PD (75.0%), with *Mycobacterium intracellulare* being the most common species (56.3%), which was consistent with previous reports [12]. The most prominent clinical symptoms were cough/sputum production (76.3%) and bronchiectasis (58.8%). The main CT features included centrilobular nodules, bronchiectasis, and pulmonary cavities, all of which were consistent with the imaging characteristics of NTM-PD described in the literature [13-16].

Regarding serum inflammatory factors, the present study observed that levels of CRP, TNF-α, IL-6, HMGB1, Cys C, and CA19-9 in patients with NTM-PD were significantly higher than those in the Non-ATB control group, revealing a pronounced inflammatory state in patients with NTM-PD. Previous studies had reported elevated levels of CRP and CA19-9 in patients with NTM-PD [17, 18], and the findings of the present study confirmed this. However, Hur et al. had found that TNF-α levels differed between active pulmonary tuberculosis and NTM-PD [19]. Although TNF-α levels were elevated in the NTM-PD group compared to the Non-ATB control group in the present study, the discriminative value for differential diagnosis was not entirely consistent with other studies. This discrepancy might be related to differences in control group selection, ethnicity, or sample size, and future studies with larger samples are needed for validation.

The most important finding of the present study was that serum levels of CRP, IL-6, IL-8, HMGB1, Cys C, and CA19-9 were positively correlated with the formation of pulmonary cavities, and HMGB1 and CA19-9 were identified as independent predictors. Cavities represent an important marker of disease severity and progression in NTM-PD. The mechanisms underlying cavity formation involve chronic granulomatous inflammation, tissue necrosis, and poor airway drainage. The findings of the present study suggested that these inflamma-

Table 2. Multivariate logistic regression analysis of factors influencing lung cavity formation in patients with NTM-PD

Variable	β	SE	Wald	OR (95% CI)	*P* value
HMGB1 (ng/mL)	0.133	0.046	8.341	1.142 (1.043-1.250)	0.004
CA19-9 (U/mL)	0.065	0.024	7.344	1.067 (1.018-1.118)	0.007
Bronchiectasis (present vs. absent)	0.986	0.465	4.495	2.681 (1.076-6.684)	0.034
CRP (mg/L)	0.018	0.021	0.735	1.018 (0.977-1.061)	0.391
IL-6 (pg/mL)	0.005	0.008	0.391	1.005 (0.990-1.021)	0.532
IL-8 (pg/mL)	0.003	0.005	0.360	1.003 (0.993-1.013)	0.549
Cys C (mg/L)	0.412	0.318	1.679	1.510 (0.809-2.818)	0.195
Age (years)	0.015	0.022	0.465	1.015 (0.972-1.060)	0.495
Sex (male vs. female)	-0.218	0.482	0.205	0.804 (0.313-2.068)	0.651

Note: OR, odds ratio; CI, confidence interval.

tory factors might promote lung parenchymal destruction and cavity formation [20]. HMGB1 was a late inflammatory mediator that binds to TLR4, activates the NF-κB pathway, and further releases cytokines such as IL-6 and IL-8, thereby forming an inflammatory amplification loop [21, 22]. This mechanism could explain the positive correlations observed in the present study between HMGB1 and IL-6/IL-8, which exacerbate lung tissue injury. CA19-9 was a mucinous glycoprotein whose expression increased in epithelial cells during chronic pulmonary inflammation and fibrosis. Elevated CA19-9 levels might reflect repeated epithelial repair and inflammatory injury processes [23, 24]. Cys C was associated with inflammation and tissue remodeling, and its correlation with tuberculous cavity formation had been previously demonstrated [25, 26]; similar results were obtained for NTM-PD in the present study. IL-6 and IL-8, as important chemotactic and activating factors, recruited neutrophils and released proteolytic enzymes, thereby exacerbating the destruction of cavity walls [27, 28]. Therefore, combined detection of these serum factors was helpful for the non-invasive assessment of the risk of pulmonary cavity formation.

The present study had several limitations: (1) It was a single-center retrospective study with a relatively small sample size, which might have introduced selection bias, and generalizability of the conclusions requires caution. (2) Only baseline serum inflammatory factor levels before treatment were analyzed, and dynamic changes during treatment were not monitored; therefore, the predictive value for treatment response could not be assessed. (3) A normal healthy control group was lacking, and other potential confounding factors could not be completely excluded. (4) The identification of pulmonary cavities relied on manual interpretation of CT images, and quantitative assessment of cavity volume or wall thickness was not performed. (5) Some inflammatory factors (such as TNF-α and PCT) did not show significant differences between groups, which might be related to the timing of measurement, assay sensitivity, or sample storage conditions. (6) The ROC analysis and multivariate analysis were not externally validated, and the diagnostic cutoff values and independent risk roles require confirmation by prospective studies.

In conclusion, the present study demonstrated that patients with NTM-PD CT had imaging that revealed that the main radiological features were central nodules within lobules and bronchiectasis. Serum IFs, including CRP, TNF-α, IL-6, HMGB1, Cys C, and CA19-9, were elevated in NTM-PD patients, with CRP, IL-6, IL-8, HMGB1, Cys C, and CA 19-9 showing associations with the formation of pulmonary cavities. Independent association of serum inflammatory factors, particularly HMGB1 and CA19-9, were found and they were closely associated with pulmonary cavity formation in NTM-PD and may serve as non-invasive biomarkers for assessing disease severity. Future multicenter, prospective cohort studies that integrate microbiological and imaging findings are needed to establish a more accurate evaluation system for NTM-PD activity.

Disclosure of conflict of interest

None.

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