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Distinct Clinical Features of Pulmonary Nocardiosis in Immunocompromised Patients

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Background: Pulmonary nocardiosis (PN) is a rare opportunistic infection. This study analyzed clinical differences between immunocompetent and immunocompromised PN patients and identified risk factors in the immunocompromised group to aid in early diagnosis and targeted treatment.

Methods: We retrospectively enrolled patients diagnosed with PN at our hospital from May 2015 to May 2026, categorizing them into immunocompromised (n=9) and immunocompetent (n=19) groups. We collected demographic, medical, clinical, microbiological, hematological, and chest imaging data. Univariate analysis compared group differences, while multivariate logistic regression identified independent risk factors for PN in immunocompromised patients.

Results: The study involved 28 PN patients (18 males, 10 females, average age 62). Three had disseminated infections, and 25 had non-disseminated infections. There were 19 immunocompetent and 9 immunocompromised patients. The immunocompromised group had more hematological diseases (P=0.006) and less bronchiectasis (P=0.004). They also showed less cough (P=0.026) and sputum production (P=0.014). Nocardia farcinica was the most common pathogen, found in 10 cases, followed by N. cyriacigeorgica in 9 cases, with N. farcinica prevalent in both groups. Aspergillus was more frequent in the immunocompromised group (P=0.017). The neutrophil-to-lymphocyte ratio (NLR) was higher in the immunocompromised group (P=0.022). Radiologically, bronchiectasis occurred less frequently in the immunocompromised group than in the immunocompetent group (P=0.004). The median hospitalization duration was significantly longer in the

immunocompromised group (P=0.042). Multivariate logistic regression analysis indicated that concomitant hematological disease (OR=5.122, P=0.024) and *Aspergillus* co-infection (OR=4.976, P=0.026) were independent risk factors for PN in immunocompromised patients.

Conclusions: The clinical manifestations of PN in immunocompromised patients are often atypical. Hematological disorders and concurrent *Aspergillus* infections are recognized as independent high-risk factors within this population. Therefore, it is imperative to maintain a heightened vigilance for the potential onset of nocardiosis in the lungs of these high-risk individuals, as well as to implement early screening and intervention strategies.

Key words: Clinical characteristics; Risk factors; Pulmonary nocardiosis; Immunocompromised patients

Background

Nocardia is a Gram-positive, aerobic actinomycete ubiquitously found in environmental reservoirs such as soil, sewage, and decaying organic matter[1]. It is an opportunistic pathogen capable of causing pulmonary, cutaneous, central nervous system, or disseminated infections in immunocompromised patients[2]. With the widespread application of organ transplantation, tumor radiotherapy and chemotherapy, as well as glucocorticoids or immunosuppressants for autoimmune diseases, the proportion of immunocompromised hosts has been increasing year by year, and the detection rate of pulmonary nocardiosis (PN) has been on the rise[3–5]. Moreover, *Nocardia* infections can occur in individuals with intact immune systems. Several studies suggest that immunocompetent hosts constitute approximately 40% to 60% of cases[6,7]; these patients often have underlying conditions such as chronic pulmonary diseases[8].

At present, the sample size of comparative studies on PN in immunocompromised and immunocompetent patients is limited, and the differences in clinical characteristics and high-risk pathogenic factors between the two groups have not been fully clarified. Therefore, we described and analyzed the clinical data of 28 patients with PN, explored the independent risk factors for PN in immunocompromised patients, and optimized the clinical screening strategies for high-risk populations.

Materials and methods

Study population and design

A retrospective study was conducted on 28 patients diagnosed with PN at Beijing Tsinghua Changgung Hospital from May 2015 to May 2026. All enrolled participants were classified as having confirmed PN if they met the following diagnostic criteria[9,10]: (1) a positive microbial culture or metagenomic next-generation sequencing (mNGS) results obtained from sputum or bronchoalveolar lavage fluid (BALF); (2) imaging findings on thoracic computed tomography or chest radiography that corresponded with the characteristic manifestations of PN; and (3) clinical symptoms indicative of a lower respiratory tract infection, including cough,

expectoration, dyspnea, and a body temperature exceeding 38.3°C. These patients were divided into two groups based on their immune status: the immunocompetent group (19 cases) and the immunocompromised group (9 cases). Individuals are considered to have immunocompromised status if they satisfy one or more of the following conditions[11]: (1) use of glucocorticoids (≥20 mg/day of prednisone equivalent) lasting ≥14 days or cumulative dosage of 600 mg, use of disease-modifying anti-rheumatic drugs, biological response modifiers, or other immunosuppressive agents for over 30 days；(2) presence of active malignancy or receipt of chemotherapy for cancer；(3) history of solid organ transplantation；(4) history of hematopoietic stem cell transplantation；(5) Diagnosis of primary or acquired immune deficiency.

Data collection

We selected qualified data from the hospital's medical record system, including the demographic data, clinical characteristics (smoking history, drinking history, complications, and symptoms), laboratory examination results (white blood cell count (WBC), neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), hemoglobin, platelet count, lactate dehydrogenase (LDH), hypersensitive C-reactive protein (HsCRP), erythrocyte sedimentation rate (ESR), etc.) within 24 hours after diagnosis of PN, co-infection pathogens, imaging features, treatments, and outcomes of the patients.

Statistical Analysis

For continuous variables, non-normally distributed data were summarized as the median with interquartile range (IQR), while normally distributed data were presented as the mean ± standard deviation (SD). Between-group comparisons for continuous variables were performed using the Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Categorical variables were described as percentages (%), and group differences were evaluated using the Chi-square test or Fisher's exact test, depending on sample size and expected frequency assumptions. Statistical significance was defined as a P-value < 0.05. In univariate analyses, covariates with $P < 0.05$ were selected for inclusion in the final

multivariable logistic regression model to identify independent predictors while controlling for confounding factors. All statistical analyses were conducted using IBM SPSS statistics version 29.0 (IBM Corp. USA) and Graphpad Prism 10.

Results

Demographic characteristics and baseline data of pulmonary nocardiosis patients

The study encompassed 28 patients diagnosed with PN, consisting of 18 males and 10 females, with an average age of 62 years. Among these patients, three cases were identified as disseminated infections, while 25 were classified as non-disseminated. According to the different immune statuses, they were divided into the immunocompetent group (n=19) and immunocompromised group (n=9).

As shown in **Table 1**, the median length of hospital stay for the immunocompromised group was longer than that of the immunocompetent group (24 vs 16, P=0.042). Baseline comorbidities indicated a significantly higher proportion of hematological diseases (44% vs 0, P=0.006) and less proportion of bronchiectasis (11.1% vs 73.7%, P=0.004) within the immunocompromised group. There were no statistically significant differences in gender composition, age, smoking and drinking history, pneumonia severity index (PSI) classification, incidence of respiratory failure, and rate of extrapulmonary organ involvement between the two groups.

Clinical characteristics of pulmonary nocardiosis in immunocompromised and immunocompetent patients

As presented in **Table 2-1**, in terms of clinical symptoms of PN patients, the proportions of fever, hemoptysis, dyspnea, chest pain and headache were not statistically different between the two groups. The proportions of cough (55.6% vs 94.7%, P=0.026) and expectoration (22.2% vs 78.9%, P=0.014) in the immunocompromised group were significantly lower than those in the immunocompetent group.

In terms of pathogen distribution, *Nocardia farcinica* (*N. farcinica*) was the most prevalent species, identified in 10 cases, followed by *N. cyriacigeorgica,* identified in 9cases; notably, *N. farcinica* was the most frequently isolated species in

immunocompromised group and the immunocompetent group. There was no statistical difference in the different subspecies of *Nocardia* between the two groups (**Figure 1**). Etiological examination results showed that patients in the immunocompromised group had a higher proportion of co-infection with *Aspergillus* infection than those in the immunocompetent group (44.4% vs 5.3%, P=0.017)（**Figure 2, 3**）. In the immunocompetent group, the proportion of Gram-negative bacteria infection was the highest (21.1%), followed by fungi (15.8%) and Gram-positive bacteria (5.3%). In the immunocompromised group, the proportion of patients with fungal infections was the highest (44.4%), followed by Gram-negative bacteria (33.3%), and Gram-positive bacteria (11.1%). There was no significant difference in the proportion of bacterial infection between the two groups. In terms of pathogen detection, there was no statistically significant difference between the two groups in terms of sputum or BALF culture, or mNGS testing.

Laboratory findings revealed the NLR was significantly elevated in the immunocompromised group compared with the immunocompetent group (5.9 vs. 2.5，P = 0.022). There was no statistically significant differences between the two groups in WBC, neutrophil count, lymphocyte count, hs-CRP, ESR, serum albumin, or LDH. In terms of imaging, patients in the immunocompetent group had a higher proportion of bronchiectasis than those in the immunocompromised group (73.7% vs 11.1%, *P*=0.004), while there was no statistical difference between the two groups in the proportion of patchy opacities, nodules, mass, cavity, ground-glass opacities, pleural effusion, consolidation, or mucus plugs, as shown in **Table 2-2**, **Figure 4**.

Multivariate analysis of pulmonary nocardiosis in immunocompromised patients

In the multivariate logistic regression analysis, variables with a P-value＜0.05 in the univariate screening including length of hospital stay, hematologic malignancies, bronchiectasis, cough, sputum production, *Aspergillus* co-infection, and the NLR were incorporated into the model. Following adjustment for potential confounders, hematologic malignancies (OR=5.122, 95%CI 0.538-21.887, P=0.024) and *Aspergillus* co-infection (OR=4.976, 95%CI 0.439-14.495, P=0.026) remained statistically significant. These factors were identified as independent risk factors for

PN among immunocompromised patients, as detailed in **Table 3**.

Discussion

PN is a prototypical opportunistic infectious disease, with its incidence being intricately linked to the immune status of the host[12,13]. The majority of patients with *Nocardia* infections exhibit compromised immune function, primarily due to factors such as glucocorticoid therapy, malignancies, organ transplantation, hematopoietic stem cell transplantation, and AIDS[14]. However, approximately one-third of those infected are immunocompetent, although they frequently present with underlying structural lung conditions, such as chronic obstructive pulmonary disease and bronchiectasis[15,16]. This study stratified patients according to their immune status and conducted a comparative analysis of clinical data from 28 individuals diagnosed with PN. A systematic analysis was performed to elucidate the clinical heterogeneity between immunocompetent and immunocompromised patients, identifying independent risk factors associated with the disease in the immunocompromised patients. The findings of this research enhance the understanding of the characteristics of PN across different immune status groups, thereby providing a clinical foundation for the tailored screening and early intervention of high-risk populations.

The study revealed that bronchiectasis was the predominant underlying pulmonary condition in immunocompetent patients with PN, accounting for 73.7% of cases, whereas its prevalence in the immunocompromised group was only 11.1%. This intergroup difference was statistically significant (P=0.004). Building upon prior research, it is evident that bronchiectasis can lead to irreversible damage to the anatomical structure of the airways, diminish the ciliary clearance capability, result in secretion retention, and progressively weaken the local defense barrier[17]. These alterations create favorable conditions for the environmental invasion and proliferation of *Nocardia*. At the same time, the infection caused by *Nocardia* itself may lead to a further aggravation of bronchiectasis[18–20]. This may represent the underlying pathophysiological mechanism by which chronic structural lung diseases have emerged as the leading cause of respiratory infection among immunocompetent

individuals. In contrast, 44.4% of patients with immunodeficiency had concomitant hematological disorders a proportion significantly higher than that observed in the immunocompetent group (P = 0.006). Multivariate analysis identified hematological disorders as an independent risk factor for PN infection in this cohort. These disorders inherently impair both cellular and humoral immune homeostasis. Furthermore, the reduction of lymphocyte caused by treatment methods such as radiotherapy and chemotherapy further led to a significant decline in the overall defense ability of the body against pathogenic bacteria[21,22]. The compromised immune system markedly increases the susceptibility of this group to *Nocardia* infections.

Patients with compromised immune systems often exhibit atypical or reduced respiratory symptoms, which can lead to delays in diagnosis[23]. Univariate analysis demonstrated significantly higher incidences of cough and sputum production in the immunocompetent patients (P<0.05). Individuals with intact immunity often present with bronchiectasis and exhibit typical symptoms of airway inflammation[24]. Conversely, in patients with compromised immunity, the airway structure may remain intact, but immune deficiency predominates, leading to a diminished inflammatory response and atypical clinical manifestations[23]. The duration of hospital stay is significantly longer for the compromised immunity group compared to those with normal immunity (24 days vs. 16 days, P=0.042). There was no difference in imaging signs such as pulmonary patchy shadows, nodules, cavities, and consolidation between the two groups; only the imaging of bronchiectasis was consistent with the distribution of underlying pulmonary diseases, suggesting that even if there was no obvious cough or expectoration in immunocompromised patients, pulmonary lesions of unknown cause also needed to be screened for PN[9,25]. This study demonstrated that the NLR was significantly elevated in the immunocompromised group (P=0.022), while no differences were observed in conventional inflammatory markers between the groups. An increased NLR may indicate an immune imbalance[26]. Nevertheless, after controlling for multiple confounding variables, cough, expectoration, and the NLR did not demonstrate statistical significance within the patients. This suggests that these indicators are not independent predictors of disease risk in

immunocompromised individuals. Clinically, it is imperative to consider a combination of factors, including underlying diseases and concurrent infections, to achieve a comprehensive assessment.

Mixed infections represent a critical concern in the diagnosis and management of PN among immunocompromised patients[3,27]. This study identified a co-infection rate of *Aspergillus* in immunocompromised patients at 44.4%, markedly higher than the 5.3% observed in immunocompetent individuals (P=0.017). Multivariate analysis further established *Aspergillus* co-infection as an independent risk factor for disease in immunocompromised patients. Both *Nocardia* and *Aspergillus* are classified as environmental opportunistic pathogens, and in immunocompromised hosts, they frequently engage in dual infections[28]. The interactions among these pathogens not only elevate the risk of infection and complicate clinical management but are also associated with the mortality in immunocompromised patients[28,29]. In light of these findings, for immunocompromised patients diagnosed with pulmonary aspergillosis who exhibit no lesion absorption following standardized antifungal therapy and whose symptoms persist in worsening, it is imperative to promptly perform *Nocardia* pathogen detection in sputum and BALF. This approach facilitates the early identification of mixed infections and enables the optimization of the anti-infective treatment regimen[30].

This study is subject to several limitations. Firstly, it is a single-center retrospective analysis, which constrains the capacity to establish causal relationships. Secondly, the sample size is relatively small, introducing potential selection bias. Consequently, the findings necessitate further validation through multi-center, large-sample prospective studies. Thirdly, the follow-up period was limited to the duration of hospitalization, with no long-term follow-up conducted, potentially limiting a comprehensive understanding of patient prognosis.

In conclusion, hematological diseases and and combined aspergillus infection are independent risk factors for PN in immunocompromised individuals. For these high-risk groups, it is imperative to establish targeted screening strategies. This includes shifting away from the conventional diagnostic focus on "typical respiratory

symptoms" and integrating NLR testing, chest imaging, and multi-pathogen screening into routine assessments. Specifically, for immunocompromised patients with persistent pulmonary lesions due to *Aspergillus* infection, emphasis should be placed on screening for mixed *Nocardia* infections. Such measures are essential to facilitate early diagnosis, enable precise treatment, and ultimately enhance patient outcomes.

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Ethics Approval and Informed Consent

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Ethics Committee of the Beijing Tsinghua Changgung Hospital-approval: No.23617-0-03. Adult participant consent was not required because this was a retrospective study, the requirement for informed consent was waived by the ethics committee.

Clinical trial number

Not applicable

Declaration of Competing Interest

The authors report no conflicts of interest in this work.

Table legends：

Table 1. Demographics of pulmonary nocardiosis in immunocompromised patients

Table 2-1. Clinical features of pulmonary nocardiosis in immunocompromised patients

Table 2-2. Laboratory finding and chest CT imaging features of pulmonary nocardiosis in immunocompromised patients

Table 3. The multivariate logistic analysis for risk factors associated with of pulmonary nocardiosis in immunocompromised patients

Figure legends:

Figure 1. The distribution of different types of *Nocardia* in the immunocompetent group and the immunocompromised group

Figure 2. The composition of pathogens in patients with normal immunity and those

with compromised immunity who have pulmonary nocardiosis. (A) Composition of pathogens in all enrolled patients; (B) Immunocompetent group; (C) Immunocompromised group

Figure 3. The composition of fungal infection in immunocompetent and immunocompromised pulmonary nocardia disease patients.

Figure 4. Chest imaging findings in patients with pulmonary nocardiosis complicated by aspergillosis. (A,B). Well defined, mass like high attenuation opacities are present in the left upper lobe and right lower lobe; these lesions contain multiple irregularly shaped, air filled cavities. (C). Patchy areas of consolidation and irregular, non-calcified nodules are observed in the right middle lobe and left lower lobe. (D). Bronchiectasis is bilaterally, exhibiting both cystic and cylindrical morphologies; some dilated bronchi contain mucus plugs. Concurrent bronchial wall thickening and peribronchial ground glass opacities are noted.

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Table 1. Demographics of pulmonary nocardiosis in immunocompromised patients

Variable	Immunocompetent (n=19)	Immunocompromised (n=9)	*P*-value
Sex (male), n (%)	10 (52.6)	8 (88.9)	0.148
Age [a], median (IQR)	63 (56, 68)	59 (37, 63.5)	0.105
Tobacco use, n (%)	4 (21.1)	3 (33.3)	0.646
Drinking history, n (%)	4 (21.1)	1 (11.1)	1.000
Hospital day, median(IQR)	16 (12, 23)	24 (18.5, 59)	0.042*
PSI risk classes, n (%)			
II	11 (57.9)	4 (44.4)	0.794
III	6 (31.6)	3 (33.3)	1.000
IV-V	2 (10.5)	2 (22.2)	0.574
Respiratory Failure, n (%)	3 (15.8)	2 (22.2)	1.000
Involving organs other than the lungs, n (%)	1 (5.3)	2 (22.2)	0.234
Non-pulmonary underlying deseases, n(%)			
Solid tumor	0 (0)	1 (11.1)	0.321
Hematological system diseases	0 (0)	4 (44.4)	0.006*
Kidney transplantation	0 (0)	2 (22.2)	0.095
Conorary heart disease	2 (10.5)	1 (11.1)	1.000
Autoimmune disease	1(5.3)	3 (33.3)	0.084
Hypertension	2 (10.5)	3 (33.3)	0.290
Diabetes mellitus	3 (15.8)	2 (22.2)	1.000
Pulmonary underlying deseases, n(%)			
Lung cancer	0 (0)	1 (11.1)	0.321
Bronchiectasis	14 (73.7)	1 (11.1)	0.004*
COPD	4 (21.1)	0 (0)	0.273
Asthma	3 (15.8)	0 (0)	0.530
Chronic pulmonary thromboembolism	2 (10.5)	0 (0)	1.000
Sarcoidosis	0 (0)	1 (11.1)	0.321
Inactive tuberculosis	6 (31.6)	1 (11.1)	0.371

Note：[a]：Median (IQR); * $P<0.05$, denotes statistically significant difference.

Table 2-1. Clinical features of pulmonary nocardiosis in immunocompromised patients

Variable	Immunocompetent (n=19)	Immunocompromised (n=9)	*P*-value
Symptoms , n (%)			
Fever	7 (36.8)	4 (44.4)	1.000
Cough	18 (94.7)	5(55.6)	0.026*
Sputum	15 (78.9)	2 (22.2)	0.014*
Haemoptysis	2 (10.5)	1 (11.1)	1.000
Dyspnea	8 (42.1)	3 (33.3)	0.976
Chest pain	2 (10.5)	0 (0)	1.000
Headache	1 (5.3)	0 (0)	1.000
Co-infection pathogens, n (%)			
Bacterial infection			
Gram-negative bacteria	4 (21.1)	3 (33.3)	0.646
Gram-positive bacteria	1 (5.3)	1 (11.1)	1.000
Fungal infection			
Aspergillus	1 (5.3)	4 (44.4)	0.017*
Mucorales	2 (10.5)	0 (0)	1.000
Pneumocystis jirovecii	0 (0)	1 (11.1)	0.321
Culture, n (%)			
Sputum	4 (21.1)	2 (22.2)	1.000
BALF	6 (31.6)	0 (0)	0.136
mNGS, n (%)			
BALF	14 (73.7)	9 (100)	0.144

Note：* $P<0.05$, denotes statistically significant difference. **BALF**: Bronchoalveolar lavage fluid, **mNGS:** Metagenomic next-generation sequencing

Table 2-2. Laboratory finding and chest CT imaging features of pulmonary nocardiosis in immunocompromised patients

Variable	Immunocompetent (n=19)	Immunocompromised (n=9)	*P*-value
Laboratory parameters			
White blood cell count [a] (×10^9/L)	7.2（5.1, 10.5）	7.7 (4.8,11.1)	1.000
Neutrophil count [a] (×10^9/L)	3.9 (3.0, 7.3)	6.6 (2.8, 9.1)	0.847
Lymphocyte count [b] (×10^9/L)	1.8±0.7	1.3±1.3	0.211
NLR [a]	2.5 (1.8, 5.5)	5.9 (3.7, 12.4)	0.022*
Hemoglobin [a] (g/L)	134 (122, 143)	122(106, 132.5)	0.105
Platelet count [b] (×10^9/L)	261.7±75.8	257±91.8	0.902
Hypersensitive C-reactive protein [a] (mg/L)	32.3 (2.2, 73.0)	13.1 (4.7,26.2)	0.468
Erythrocyte sedimentation rate [a] (mm/h)	29 (17, 59)	27 (17, 71.75)	0.887
Albumin [b] (g/L)	39.7±3.8	37.3±2.7	0.095
Lactate dehydrogenase [a] (IU/L)	162 (154, 192)	200 (153.5, 261)	0.054
Imaging features, n (%)			
Patchy opacities	6 (31.6)	2 (22.2)	0.949
Nodules	10 (52.6)	4 (44.4)	1.000
Mass	1 (5.3)	0 (0)	1.000
Cavity	4 (21.1)	2 (22.2)	1.000
GGO	0 (0)	2 (22.2)	0.095
Pleural effusion	1 (5.3)	2 (22.2)	0.234
Bronchiectasis	14 (73.7)	1 (11.1)	0.004*
Consolidation	10 (52.6)	7 (77.8)	0.391
Mucus plugs	3 (15.8)	2 (22.2)	1.000

Note：[a]：Median (IQR); [b]: mean ± standard deviation; * $P<0.05$, denotes statistically significant difference. NLR：Neutrophil/Lymphocyte Ratio.

Table 3. The multivariate logistic analysis for risk factors associated with of pulmonary nocardiosis in immunocompromised patients

	Multivariate analysis		
	OR	95% CI	***P*-value**
Hospital day	0.688	-9.340-27.423	0.637
Hematological system diseases	5.122	0.538-21.887	0.024*
Bronchiectasis	2.093	-15.513-0.902	0.148
Cough	1.120	-31.910-3.121	0.290
Sputum	1.664	-1.425-15.367	0.197
Aspergillus	4.976	0.439-14.495	0.026*
NLR	0.119	-0.876-0.455	0.730

Note: * $P < 0.05$, indicating statistically significant difference.

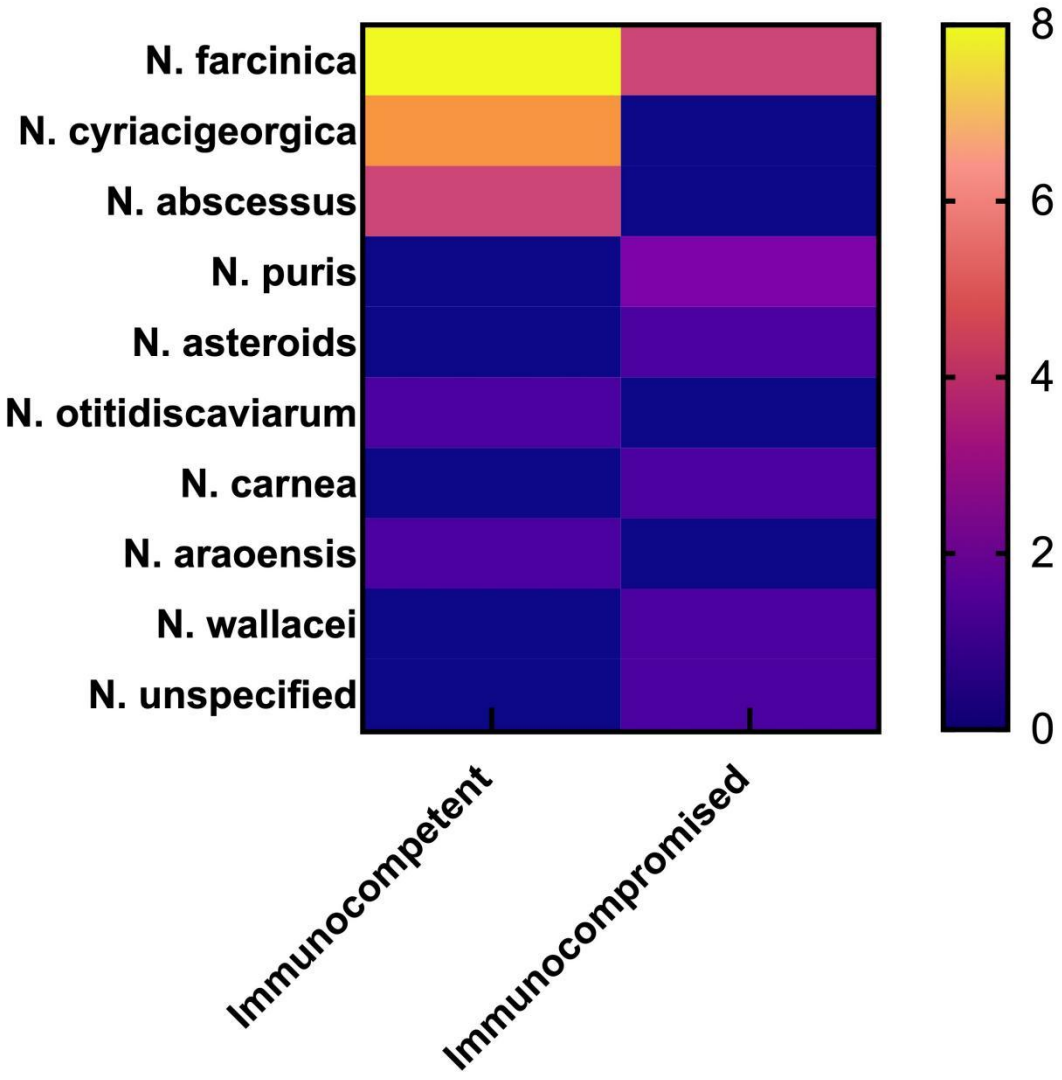


Figure 1. The distribution of different types of *Nocardia* in the immunocompetent group and the immunocompromised group

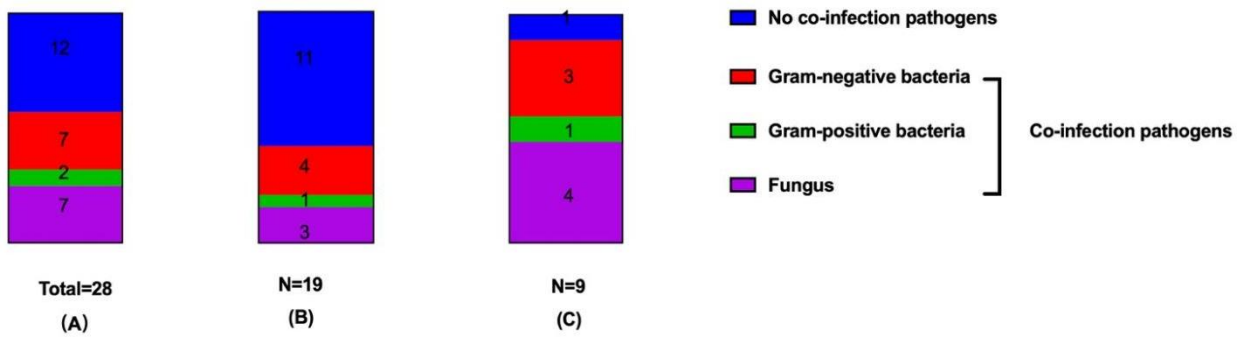


Figure 2. The composition of pathogens in patients with normal immunity and those with compromised immunity who have pulmonary nocardiosis. (A) Composition of pathogens in all enrolled patients; (B) Immunocompetent group; (C) Immunocompromised group

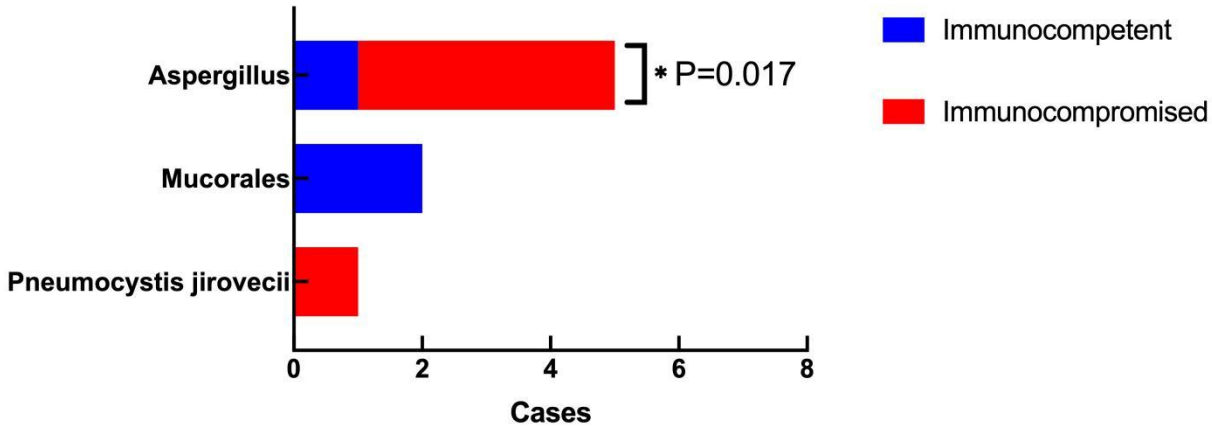
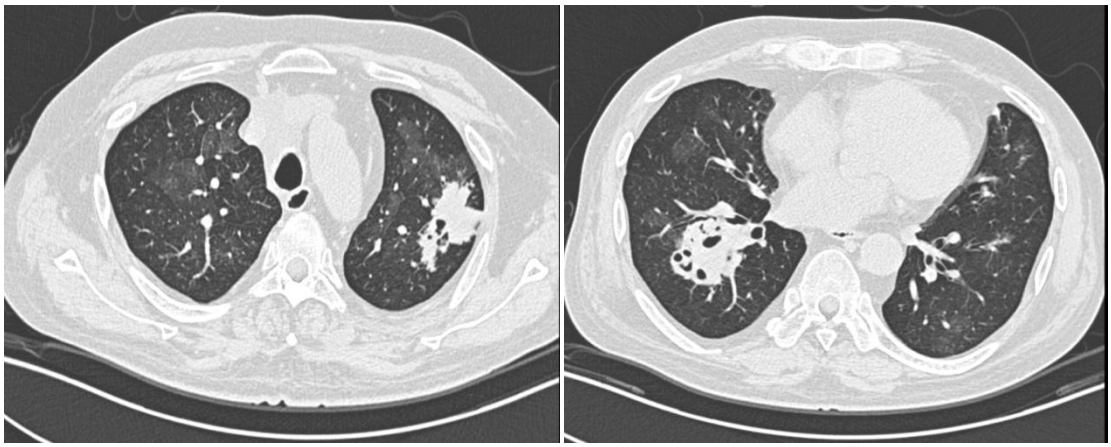
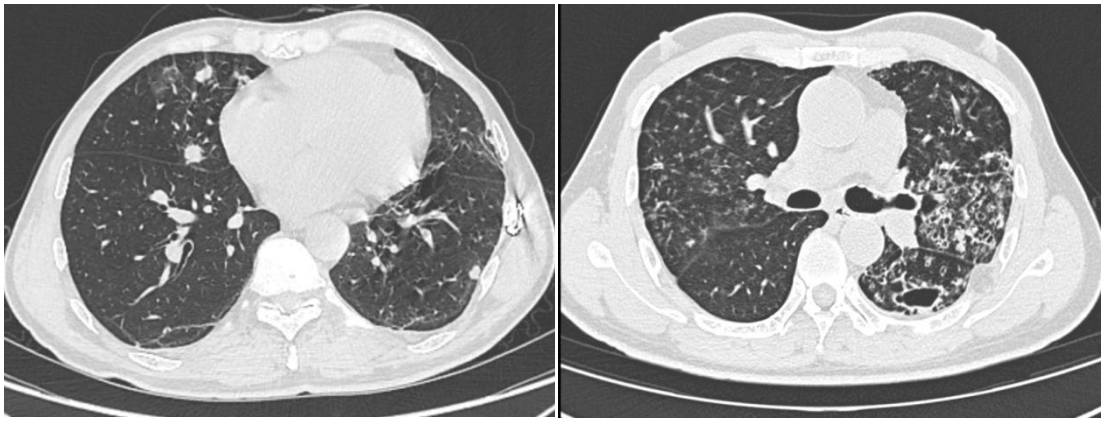


Figure 3. The composition of fungal infection in immunocompetent and immunocompromised pulmonary nocardia disease patients.



(A) (B)



(C) (D)

Figure 4. Chest imaging findings in patients with pulmonary nocardiosis complicated by aspergillosis. (A,B). Well defined, mass like high attenuation opacities are present in the left upper lobe and right lower lobe; these lesions contain multiple irregularly shaped, air filled cavities. (C). Patchy areas of consolidation and irregular, non-calcified nodules are observed in the right middle lobe and left lower lobe. (D). Bronchiectasis is bilaterally, exhibiting both cystic and cylindrical morphologies; some dilated bronchi contain mucus plugs. Concurrent bronchial wall thickening and peribronchial ground glass opacities are noted.