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ORIGINAL ARTICLE

# Pulmonary nocardiosis in southern Taiwan

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**KEYWORDS**
*Nocardia* species;
Outcome;
Pulmonary nocardiosis;
Radiographic findings

*Background/Purpose:* Nocardiosis mainly affects immunocompromised patients. The objectives of this study were to better understand the epidemiologic, demographic, clinical, and laboratory information in patients with pulmonary nocardiosis in southern Taiwan.
*Methods:* Retrospective analyzing patients aged ≥18 years with culture-proven pulmonary nocardiosis received treatment at KCGMH between January 2004 and June 2010. Nocardiae were identified by 16S rRNA gene sequence analysis. Patients with pulmonary nocardiosis caused by the mostly commonly encountered *Nocardia* sp. were compared with those with pulmonary nocardiosis due to other *Nocardia* spp.
*Results:* Among the 20 patients included, cough (80%) and fever (50%) were the 2 leading symptoms/signs, while lobar consolidation (50%) and pleural effusion (40%) were the most frequent radiographic manifestations. Eighteen patients (90%) had at least one underlying disease/condition. *Nocardia cyriacigeorgica* was most commonly found. Compared with those whose pathogens were other *Nocardia* spp., patients with pulmonary nocardiosis caused by *N cyriacigeorgica* experienced higher clinical severity as measured by APACHE II score (19.8 ± 7.0 vs. 12.8 ± 6.7; $p = 0.04$) and ICU admission rate (100% vs. 25%; $p < 0.01$). Thirteen patients (65%) turned out to be fatal. The severity (APACHE II score, 18 ± 6 vs. 10 ± 8; $p = 0.02$) and the proportion of acute and subacute pulmonary nocardiosis (76% vs. 0%, $p = 0.03$) between fatal and survived patients differed significantly.

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*Conclusions:* *N cyriacigeorgica* was the most common pathogen in southern Taiwan. Higher mortality rate in patients with pulmonary nocardiosis was related to disease severity and acute and subacute infection.


## Introduction

Nocardiosis is an opportunistic infection that mainly affects patients with compromised cell-mediated immunity, such as those experiencing long-term steroid use, with acquired immunodeficiency syndrome (AIDS), or being recipients of organ transplantation.[1,2] Nocardiosis has a wide range of clinical presentations, and pulmonary involvement is most commonly encountered.[3] *Nocardia* spp. are widely distributed in soil and water, and on vegetable matter. This may become airborne on dust particles leading to pulmonary infection in immunocompromised patients via inhalation. Pulmonary nocardiosis usually results in high mortality and morbidity if it is not diagnosed early enough for starting a timely treatment.[1,2,4] However, an early diagnosis of pulmonary nocardiosis may be difficult and challenging because signs and symptoms in the affected patients are nonspecific. A high index of clinical suspicion of nocardiosis is, therefore, necessary.[5]

The taxonomy of *Nocardia* has been evolving because the introduction of molecular methods, such as 16S rRNA gene sequence analysis, leads to better classification.[3,6] The prevalence of individual *Nocardia* species may differ from one geographical location to another, probably depending upon local climate.[6] Little is known about nocardiosis in southern Taiwan thus far. We conducted a retrospective study in patients with pulmonary nocardiosis at Kaohsiung Chang Gung Memorial Hospital (KCGMH), with the objectives to better understand the epidemiologic, demographic, clinical, and laboratory information in this patient population in southern Taiwan. The pathogenic *Nocardia* isolates were identified to their species level using 16S rRNA gene sequence analysis, which was usually not performed in most clinical laboratories at daily practice. As a substantial number of reports suggested the predominance of one specific *Nocardia* species among the culprit *Nocardia* isolates in each series,[1,6–8] for practical reasons, we carried out comparisons of difference between patients with pulmonary nocardiosis caused by the most commonly encountered *Nocardia* sp. and those with pulmonary nocardiosis due to the other *Nocardia* spp. In addition, data of patients with pulmonary nocardiosis retrieved at literature review were compared to those in our series.

## Materials and methods

### Study population

All adult (age $\geq$18 years) patients with culture-proven pulmonary nocardiosis receiving treatment at KCGMH during January 2004—June 2010 were included in this retrospective analysis. KCGMH is a 2600-bed facility serving as a primary care and tertiary referral center in southern Taiwan. Potentially eligible patients were retrieved from the hospital's clinical microbiology laboratory and were included after confirmation of pulmonary nocardiosis. A patient was included once if the culture of specimens sampled at different time points all grew *Nocardia* isolates, and the first episode and its *Nocardia* isolate was counted.

Demographic, clinical, radiographic, and laboratory data of the included patients were retrieved from the reviewed medical charts. The study was conducted with a waiver of patient consent approved by the Institution Review Board of Chang Gung Memorial Hospital, Taiwan (CGMHIRB No.100-0801B).

Data analyzed included those regarding demographics, underlying diseases/conditions (e.g., diabetes mellitus, chronic kidney disease, chronic liver disease, chronic lung disease, solid organ malignancy, hematologic disease, and history of long term steroid therapy), clinical manifestations (e.g., fever, malaise, chest pain, and cough) and severity stratified based on APACHE II score [9] and the need for admission to intensive care unit (ICU), overall mortality, chest radiographic presentations and hemogram. Chest radiographs were read by a radiologist (W.C. Lin) who also interpreted the findings in a brain computed tomography or magnetic resonance image if such was available. Annual incidences of pulmonary nocardiosis (2004—2009) at KCGMH were calculated, of which the denominators were the number of the discharged patients of the corresponding year obtained from the hospital's administrative records. A MEDLINE search and supplemental manual literature search for pulmonary nocardiosis were performed. Keywords used in literature search included nocardiosis, pulmonary nocardiosis and *Nocardia* species. Demographics, underlying diseases/conditions and prognosis of patients in this series were compared with those reported in the literature.

### Definitions

A definitive diagnosis of pulmonary nocardiosis was established based on the growth of a *Nocardia* sp. from the culture of respiratory-tract specimen(s) (i.e., sputum, endotracheal aspirate, pleural effusion, bronchoalveolar lavage, and/or biopsied lung tissue) in a patient whose clinical and chest-radiographic presentations were consistent with nocardiosis. The included patients were classified as those suffering acute, sub-acute or chronic pulmonary nocardiosis,[2,4] which referred to pulmonary nocardiosis that clinically progressed as rapidly as less than 2 weeks, between 2 weeks and 3 months, and more than 3 months, respectively. Chronic kidney disease was defined as glomerular filtration rate $<$60 mL/min/1.73 m$^2$ for more than 3 months.[10] Chronic liver disease referred to chronic viral hepatitis and alcoholic liver

disease with or without cirrhosis as was sonographically suggested. Long-term steroid usage was defined as taking at least 10 mg prednisolone or its equivalent per day for more than 2 months prior to the development of nocardiosis. Patients with clinically diagnosed bronchiectasis, chronic obstructive pulmonary disease, or pneumoconiosis coupled with consistent findings from his or her chest radiograph were considered having chronic lung disease. Empyema caused by *Nocardia* sp. referred to the growth of this pathogen from pleural effusion culture. Leukocytosis referred to a peripheral white cell count $\geq 11 \times 10^9$/L. Mortality was defined as all-cause death during the patient's hospital stay.

### Microbiological analysis

Organisms tentatively identified as *Nocardia* isolates on the basis of their ability to grow aerobically, their colonial and microscopic morphology (i.e., branching, beaded, filamentous Gram-positive bacilli), and demonstration of partial acid-fast staining,[11] were verified by partial sequencing analysis of the 16S rRNA gene of the *Nocardia* isolates using the primers 16S-27F (5'-AGAGTTTGATCCTGGCTCAG-3') and 16S-907R (5'-CCGTCAATTCCTTTGAGTTT-3')[12] The sequenced nucleotides were compared with those published in the 16S rRNA database (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The closest matches and GenBank accession number were obtained.

### Statistical analyses

The included patients were divided into two groups: those with lung infection caused by the most commonly encountered *Nocardia* sp. and those with lung infection due to other *Nocardia* spp. Variables between the two groups were compared with each other. Difference between continuous variables was assessed using the *t* test or Mann-Whitney *U* test, while difference between dichotomous variables was assessed using the Chi-square test or Fisher's exact. The linear regression was fitted to evaluate the trend in pulmonary nocardiosis rate using the *t* test. A two-tailed *p* value of $<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS software package, version 11.5 (SPSS Inc., Chicago, IL, USA).

## Results

A total of 20 patients (12 men and eight women) with pulmonary nocardiosis (mean age 65 years) were included for analysis. The trend in the annual incidence (2004–2009) of pulmonary nocardiosis is shown in Fig. 1. The annual incidence of pulmonary nocardiosis increased from 3.4 (2004–2005) to 8 (2008–2009) per 100 000 hospitalized patients at KCGMH ($p = 0.13$). These 20 patients are detailed in Table 1, and 18 (90%) of them had at least one underlying disease/condition. Demographic and clinical information of patients with pulmonary nocardiosis reported from Taiwan are summarized in Table 2. The radiographic manifestations of patients with pulmonary nocardiosis in this and other series retrieved from the literature are summarized in Table 3.

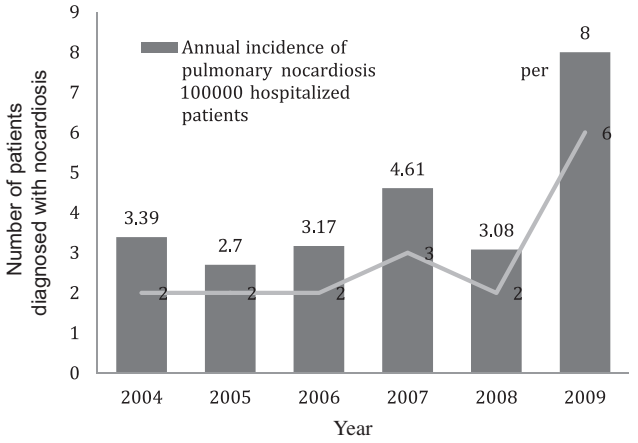


**Figure 1.** Trend in the annual incidence of pulmonary nocardiosis per 100,000 hospitalized patients in KCGMH from 2004–2009.

Among these 20 included patients, cough was found in 16 (80%), fever in 10 (50%). chest pain in 5 (25%), as well as hemoptysis and malaise each in 3 (15%). Leukocytosis was found in 10 (59%) of 17 patients with data available. Lobar consolidation (50%) and pleural effusion (40%) were most frequently found chest radiographic manifestations. Of the 8 patients with pleural effusion, 3 (15%) were diagnosed with empyema. Neutrophil predominance and elevated LDH (>200 U/L; median 1572 U/L; range 113–32,385 U/L]) were found in pleural effusion of 4 of the 6 patients who received pleurocentesis. The leading common underlying diseases in patients with pulmonary nocardiosis were chronic liver disease ($n = 7$), chronic lung disease ($n = 6$), and diabetes mellitus ($n = 6$). Brain CT was performed in 6 patients and none of them disclosed brain abscess. Among the 18 *Nocardia* isolates available and subject to identification by 16S rRNA analysis, *N cyriacigeorgica* ($n = 10$) was most commonly found, followed by *N beijingensis* ($n = 4$), *N otitidiscaviarum* ($n = 2$), *N farcinica* ($n = 1$), and *N brasiliensis* ($n = 1$).

The differences in demographics, underlying disease/condition, clinical severity and outcome of patients with pulmonary nocardiosis caused by *N cyriacigeorgica* and those with pulmonary nocardiosis due to noncryiacigeorgica *Nocardia* spp. are summarized in Table 4. Of note, significantly higher level of clinical severity was found patients with pulmonary nocardiosis caused by *N cyriacigeorgica* than those with pulmonary nocardiosis due to noncryiacigeorgica *Nocardia* spp. as was measured by APACHE II score ($19.8 \pm 7.0$ vs. $12.8 \pm 6.7$; $p = 0.04$) and by the proportion of patients mandated admission to an ICU (100% vs. 25%; $p < 0.01$). Thirteen patients (65%) turned out to be fatal, and among them, *N cyriacigeorgica* was found to be the pathogen in 8, while *N beijingensis*, *N brasiliensis*, *N farcinica*, and *N otitidiscaviarum* were each found to be a pathogen in 4 patients (Table 1). Between the fatal cases with pulmonary nocardiosis and those who survived, the clinical severity (APACHE II score, $18 \pm 6$ vs. $10 \pm 8$; $p = 0.02$) and the proportion of acute and sub-acute pulmonary nocardiosis (76% vs. 0%, $p = 0.03$) differed significantly. Of note, the overall mortality rate among

**Table 1** Detailed information of the 20 patients with pulmonary nocardiosis

| Number/ gender/age (y) | Underlying disease/condition | Clinical specimen | *Nocardia* species identification | Clinical classification | Clinical outcome |
|---|---|---|---|---|---|
| 1/F/71 | DM, CKD | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 2/M/58 | Chronic lung disease | BAL | *N beijingensis* | Chronic | Survived |
| 3/F/88 | Chronic lung disease | Endotracheal aspirate | *N beijingensis* | Acute | Died |
| 4/M/35 | Chronic lung disease | Expectorated sputum | ND | Chronic | Survived |
| 5/F/54 | Steroid use, Lung cancer | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 6/M/80 | CKD, steroid use | Pleural effusion | *N cyriacigeorgica* | Subacute | Died |
| 7/M/60 | Steroid use, Multiple myeloma | Expectorated sputum | ND | Subacute | Died |
| 8/M/75 | None | BAL | *N beijingensis* | Acute | Survived |
| 9/M/40 | CLD, steroid use, Evan's syndrome | Biopsied lung tissue. | *N brasiliensis* | Subacute | Died |
| 10/M/47 | DM | BAL | *N otitidiscaviarum* | Acute | Survived |
| 11/F/79 | CLD, chronic lung disease | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 12/F/76 | CKD, chronic lung disease | Endotracheal aspirate | *N cyriacigeorgica* | Subacute | Died |
| 13/F/91 | None | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Survived |
| 14/M/63 | CLD | Pleural effusion | *N farcinica* | Subacute | Died |
| 15/F/71 | Chronic lung disease | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 16/F/72 | DM, CLD, steroid use, idiopathic thrombocytopenic purpura | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 17/M/61 | DM, CLD | Pleural effusion | *N otitidiscaviarum* | Acute | Died |
| 18/M/69 | Chronic lung disease | BAL | *N beijingensis* | Chronic | Survived |
| 19/M/50 | DM, CLD, hepatoma | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Died |
| 20/M/60 | DM, CKD, CLD | Endotracheal aspirate | *N cyriacigeorgica* | Acute | Survived |

F = female; M = male; BAL = bronchoalveolar lavage; CKD = chronic kidney disease; CLD = chronic liver disease; DM = diabetes mellitus; ND = not done.

patients infected by *N cyriacigeorgica* or other *Nocardia* spp. did not differ significantly (80% vs. 50%; $p = 0.32$).

## Discussion

Nocardiosis mainly affects profoundly immunocompromised patients and potentially leads to catastrophic consequences. Nocardiosis may also occur in immunocompetent patients who face certain occupational hazards.[13] A recent report from Canada disclosed a significant increasing annual trend of nocardiosis incidence from 0.33 (1997 to 1998) to 0.87 (2007 to 2008) per 100,000 inhabitants ($p < 0.001$).[14] The increasing annual nocardiosis incidence disclosed by the Canadian study might result from growing immunocompromised populations and the improvement in detection and identification of *Nocardia* spp. by clinical

**Table 2** Demographics, underlying diseases/conditions, and clinical outcomes of patients with pulmonary nocardiosis in different series

| | Tuo et al[17] (2000–2004) $n = 21$ (%) | Liu et al[6] (1998–2010) $n = 26$ (%) | Present study (2004–2010) $n = 20$ (%) |
|---|---|---|---|
| Age (y) | 68 | 54.4 ± 16.2 | 64.8 ± 15.5 |
| Male:female | 15:6 | 19:7 | 12:8 |
| Underlying disease/condition | | | |
| Diabetes mellitus | 2 (9.5) | 3 (11.5) | 6 (30) |
| Chronic kidney disease | NA | 5 (19.2) | 4 (20) |
| Chronic liver disease | 1 (4.8) | 3 (11.5) | 7 (35) |
| Chronic lung disease | 11 (52.4) | 6 (23.1) | 6 (30) |
| Steroid user | 10 (47.6) | 9 (34.6) | 5 (25) |
| Solid cancer | 0 | 3 (11.5) | 2 (10) |
| Hematologic disorder | NA | 3 (11.5) | 3 (15)[a] |
| Organ transplantation | 1 (4.8) | 3 (11.5) | 0 |
| HIV/AIDS | NA | 1 (3.8) | 0 |
| Clinical outcome | | | |
| ICU admission | 14 (66.7) | NA | 13 (65) |
| Mortality | 9 (42.8) | 4/24 (16.7) | 13 (65) |

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; ICU = intensive care unit.
[a] Three patients with pulmonary nocardiosis had multiple myeloma, Evan's syndrome, or idiopathic thrombocytopenic purpura.

**Table 3** Reported chest radiographic findings of patients with pulmonary nocardiosis

| Radiographic finding | David et al[23] (before1986) $n = 21$ (%) | Hui et al[18] (1995–2000) $n = 22$ (%) | Present study (2004-2010) $n = 20$ (%) |
|---|---|---|---|
| Pleural effusion | 10 (47.6) | 4 (18) | 8 (40) |
| Pulmonary mass | 4 (19) | | |
| Pulmonary nodule | 3 (14.3) | 12 (55) | 4 (20) |
| Multiple | | 5 (23) | 4 (20) |
| Solitary | | 7 (32) | 0 |
| Consolidation | 6 (28.6) | 19 (86) | 10 (50) |
| Lobar | | 4 (18) | 10 (50) |
| Nonsegmental | | 15 (68) | 0 |
| Lung reticular infiltrates | 1 (4.7) | | 7 (35) |
| Cavitation | 8 (38.1) | 3 (13.6) | 1 (5) |

microbiology laboratories.[15] Our data did not show a significantly increasing annual trend of pulmonary nocardiosis (Fig. 1), which might result from the small number of cases being included.

Pulmonary nocardiosis may clinically be acute, subacute, or chronic.[4] Acute nocardiosis often occurs in severely immunocompromsised patients and correlates with poor prognosis.[16] Subacute lung nocardiosis, the most commonly encountered form, often clinically mimics tuberculosis, pneumocystosis, invasive fungal infection, and/or malignancy.[16] In our study, the patients with pulmonary nocardiosis presented with acute or subacute form had a poor prognosis. Reports on pulmonary nocardiosis in Taiwan between 1998 and 2010,[6] and between 2000 and 2004[17] disclosed similar demographics and underlying disease/condition among the affected patients (Table 2). The 65% mortality rate of patients with pulmonary nocardiosis in our series was higher than those reported to range from 15% to 42.8%.[1,17–19] In general, ominous factors such as high level of clinical severity, comorbidity and/or delayed starting effective antimicrobial therapy potentially lead to adverse outcomes in septic patients. It has been mentioned in the literature that misdiagnosis or delayed diagnosis of nocardiosis are often associated with poorer outcome.[20] The difficulties in comparing mortality rates of nocardiosis patients between series lie in the differences in underlying disease and/or clinical severity, and/or the appropriateness of antimicrobial agents being used. None of the previously reported series described pulmonary nocardiosis patients' clinical severity measured by the APACHE II score.[1,17–19] Antimicrobial resistance among *Nocardia* spp. varies from one report to another,[21,22] and is often not routinely tested in clinical practice, making evaluation of the appropriateness of the prescribed antimicrobial against the pathogenic *Nocardia* spp. between series impossible. Only a prospective cohort study with simultaneous clinical, microbiological and antimicrobial susceptibility evaluations will be able to unveil the attributable mortality rate of pulmonary nocardiosis.

The histopathology of lung nocardiosis varies greatly, and was reported to include acute and chronic inflammation of the pulmonary interstitium, abscess formation with necrotization, granulomatous inflammation, and/or

**Table 4** Comparison of demographic and clinical information between patients with pulmonary nocardiosis caused by *N cyriacigeorgica* and those with pulmonary nocardiosis due to other *Nocardia* species[a]

| | Patients infected by *N cyriacigeorgica* $n = 10$ (%) | Patients infected by noncyriacigeorgica *Nocardia*, $n = 8$ (%) | $p$ |
|---|---|---|---|
| Male Gender | 3 (30) | 7 (88) | 0.03 |
| Age (year ± SD) | 70.4 ± 12.6 | 62.6 ± 15.2 | 0.25 |
| Underlying disease | | | |
| Diabetes mellitus | 4 (40) | 2 (25) | 0.64 |
| Chronic kidney disease | 4 (40) | 0 | 0.09 |
| Chronic liver disease | 4 (40) | 3 (38) | 1 |
| Chronic lung disease | 3 (30) | 3 (38) | 1 |
| Steroid use | 3 (30) | 1 (13) | 0.59 |
| Solid cancer | 2 (20) | 0 | 0.48 |
| Hematologic disorder | 1 (10) | 1 (10) | 1 |
| APACHE II score | 19.8 ± 7.0 | 12.8 ± 6.7 | 0.04 |
| ICU admission | 10 (100) | 2 (25) | <0.01 |
| Overall mortality | 8 (80) | 4 (50) | 0.32 |

APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit.
[a] A total of 18 *Nocardia* isolates were available and subject to identification to their species level by 16S rRNA analysis.

progressive fibrosis[18,23,24]; the inflammatory changes may involve pleural cavity, chest wall, and lymph nodes, leading to development of empyema and bronchopleural fistula.[23] The protean histopathological manifestations of nocardiosis may account for the diversity of radiologic features of pulmonary nocardiosis (Table 3), which include reticulonodular pattern, diffuse pneumonic infiltration, consolidation, abscess formation, cavitation, pleural effusion, and pulmonary nodules.[18,23] The nonspecific and wide array of chest radiographic manifestations of pulmonary nocardiosis makes the diagnosis difficult and challenging, and thus highlighting the importance of a high suspicion index for pulmonary nocardiosis.[24] Data from our series disclosed that lobar consolidation and pleural effusion were the 2 major chest radiographic manifestations in patients with lung nocardiosis. The lung consolidation predominantly found in chest radiographs in pulmonary nocardiosis was in agreement with that previously reported.[18,23] Of note, culture-proven nocardial empyema in 3 of the 8 patients with pleural effusion underscores the importance of sampling pleural fluid for culture for the culprit pathogen once nocardiosis is suspected.

The *Nocardia* species are taxonomically expanding rapidly, with at least 90 species described to date (http://www.bacterio.cict.fr/n/nocardia.html). Approximately 30 of the *Nocardia* species have been reported to be potentially pathogenic for humans.[6] *N cyriacigeorgica* was the most common pathogen for pulmonary nocardiosis in our institute, which is situated on the southern end of this island. *N cyriacigeorgica* was first described in 2001,[25] and has been found to be pathogens in human infections in Western Europe, Greece, Turkey, Japan, Thailand, and Canada ever since. *N cyriacigeorgica* should be differentiated from *N asteroids*. However, the accurate identification of *N cyriacigeorgica* relies on molecular methods.[26] One study revealed that 35 of the 36 *N asteroides* isolates identified by conventional tests were, in fact, non-*asteroides Nocardia* spp., as confirmed by sequencing analysis of 16S rRNA gene,[6] suggesting that *N cyriacigeorgica* be considered the major *Nocardia* species in immunosuppressed patients once nocardiosis is suspected or diagnosed in the circumstances of the identification of the species level of *Nocardia* is not feasible.[6] In our study, the patients infected by *N cyriacigeorgica* had higher APACHE II score and higher ICU admission rate. Although clinically nonsignificant, a higher mortality rate was found in patients with pulmonary nocardiosis due to *N cyriacigeorgica* in this series. Muñoz et al reported that patients with nocardiosis due to *N farcinica* and *N abscessus* had a higher mortality rate.[7] *N farcinica* and *N abscessus* were less commonly encountered and were not found in our study. Further studies with larger number of cases of nocardiosis included are needed to clarify the relations between the *Nocardia* sp. and disease severity and clinical outcomes.

In summary, *N cyriacigeorgica* is the major *Nocardia* sp. in patients with pulmonary nocardiosis in southern Taiwan, and higher mortality rate in pulmonary nocardiosis was related to clinical severity and patients with acute and subacute infection. A prospective study with a much larger number sample size is needed to further understand the epidemiologic, clinical, and microbiologic information of nocardiosis, thus improving treatment for nocardiosis-affected patients.

## Conflicts of interest

All authors declare that they have no conflicts of interest relevant to this article.

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