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Mortality After Nocardiosis: Risk Factors and Evaluation of Disseminated Infection

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Background. *Nocardia* primarily infects patients who are immunocompromised or those with chronic lung disease. Although disseminated infection is widely recognized as an important prognostic factor, studies have been mixed on its impact on outcomes of nocardiosis.

Methods. We performed a retrospective cohort study of adults with culture-confirmed nocardiosis. Advanced infection was defined as disseminated infection, cavitary pulmonary infection, or pleural infection. The primary outcome was 1-year mortality, as analyzed by multivariable Cox regression.

Results. Of 511 patients with culture growth of *Nocardia*, 374 (73.2%) who had clinical infection were included. The most common infection sites were pulmonary (82.6%), skin (17.9%), and central nervous system (14.2%). In total, 117 (31.3%) patients had advanced infection, including 74 (19.8%) with disseminated infection, 50 (13.4%) with cavitary infection, and 18 (4.8%) with pleural infection. Fifty-nine (15.8%) patients died within 1 year. In multivariable models, disseminated infection was not associated with mortality (hazard ratio, 1.16; 95% CI, .62–2.16; $P = .650$) while advanced infection was (hazard ratio, 2.48; 95% CI, 1.37–4.49; $P = .003$). *N. farcinica*, higher Charlson Comorbidity Index, and culture-confirmed pleural infection were also associated with mortality. Immunocompromised status and combination therapy were not associated with mortality.

Conclusions. Advanced infection, rather than dissemination alone, predicted worse 1-year mortality after nocardiosis. *N. farcinica* was associated with mortality, even after adjusting for extent of infection. While patients who were immunocompromised had high rates of disseminated and advanced infection, immunocompromised status did not predict mortality after adjustment. Future studies should account for high-risk characteristics and specific infection sites rather than dissemination alone.

Keywords. advanced infection; disseminated infection; mortality; nocardia; nocardiosis.

Nocardia is a genus of gram-positive, partially acid-fast bacteria that primarily infect patients who are immunocompromised and those with chronic pulmonary disease [1, 2]. The estimated annual incidence of nocardiosis is as high as 0.87 cases per 100 000 people [3, 4]. One-year mortality after nocardiosis is about 25%, with factors such as extent of infection involvement and number of comorbid conditions being associated with mortality [5]. However, few studies have examined risk factors for poor outcomes in this population.

Additionally, there has been conflicting evidence regarding disseminated infection as a risk factor for mortality. Patients with disseminated infection—defined as involvement of 2 noncontiguous sites—were originally identified as high risk >50 years ago [6]. Since then, disseminated infection has been recognized as an important factor to guide therapeutic decisions, such as number of treatment agents and duration of therapy [7]. Yet, there has since been an increase in the proportion of the population with immunocompromising conditions, such as organ transplantation [8], in addition to advances in medical therapy. Recent studies have found disseminated infection to be associated with higher mortality in adjusted and unadjusted analyses [5, 9]. Conversely, contemporary studies of solid organ transplantation among recipients with nocardiosis did not find disseminated infection to predict mortality [10, 11]. One possible explanation for this discrepancy is heterogeneity in those with nondisseminated infection. Differences among patients with immunocompromising conditions, patients who are immunocompetent with chronic lung disease, and patients who are immunocompetent with predisposing exposures such as cutaneous trauma may lead to differences in infection

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phenotype—namely, some patients may have advanced or invasive infection that has not disseminated at the time of diagnosis.

In this study, we aimed to analyze potential risk factors for 1-year mortality in adjusted analyses. Additionally, we sought to determine if a novel definition of advanced *Nocardia* infection may predict outcomes better than dissemination alone.

METHODS

Study Design

We performed a multicenter retrospective cohort study of adults with nocardiosis at 3 Mayo Clinic centers in Arizona, Florida, and Minnesota from November 2011 through April 2022. These dates were chosen to correspond with the current electronic system in our microbiology laboratory to allow more complete case acquisition. Patients were obtained from microbiology culture records and screened through predetermined criteria. Inclusion criteria were age ≥18 years and culture growth of a *Nocardia* species, as well as accompanying signs, symptoms, and/or radiographic findings consistent with clinical *Nocardia* infection. Exclusion criteria were lack of culture confirmation of *Nocardia* and lack of research authorization per state statute.

Once cases were screened for inclusion, data were manually extracted from the electronic medical record. Data included demographics, comorbid conditions, presenting characteristics, radiographic characteristics, treatment variables, and post-*Nocardia* mortality. Study data were collected and managed via REDCap electronic data capture tools. Some patients have been included in separate studies—for example, 25 [12], 64 [13], and 92 [10] case patients with nocardiosis.

Identification and Susceptibility Testing

The clinical microbiology laboratory at Mayo Clinic in Rochester, Minnesota, received specimens for culture, identification, and susceptibility testing from Mayo Clinic sites. Clinical specimens were cultured in broth in mycobacterial growth indicator tubes (BACTEC MGIT 960; Becton Dickinson) and on agar biplates (Middlebrook 7H11/7H11S) incubated at 35 to 37 °C for up to 6 weeks. Positive broth was subcultured to an agar plate (Middlebrook 7H11), and isolated colony growth was identified with Sanger sequencing of a 500-bp region of the 16S rRNA gene as previously described [14]. From August 2014, matrix-assisted laser desorption/ionization–time of flight mass spectrophotometry was introduced for species identification, with Sanger sequencing being reserved for isolates unable to be identified by this technique [15, 16]. Antimicrobial susceptibility testing was performed via broth microdilution with the Trek Sensititre Rapmyco plate and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute [17, 18]. Species identification and antimicrobial susceptibility testing was routinely attempted for all *Nocardia* isolates.

Definitions

Nocardiosis was defined as culture growth of *Nocardia* with compatible signs, symptoms, and/or radiographic findings consistent with clinical infection. *Nocardia* colonization was defined as culture growth of *Nocardia* without documented signs or symptoms of clinical infection, the presence of an alternate explanation for the clinical findings, or a lack of progression after withholding treatment. The date of *Nocardia* diagnosis was the date of first culture acquisition that ultimately grew *Nocardia*. Disseminated infection was defined as involvement of at least 2 noncontiguous organs or isolated central nervous system (CNS) involvement. Advanced infection was defined as the presence of at least 1 of the following: disseminated infection, pulmonary cavitation, or pleural involvement. Pleural involvement was assessed at initial presentation and required a pleural fluid culture yielding *Nocardia*. A site of infection could otherwise be inferred by radiographic signs compatible with nocardiosis if a primary site had culture confirmation (ie, imaging consistent with brain abscess in the setting of a respiratory culture growing *Nocardia* and accompanying signs of pulmonary infection). Immunocompromised status was defined as receipt of at least 20 mg/d of prednisone-equivalent corticosteroid, receipt of other immunosuppressive medication, and/or hematopoietic stem cell transplantation (HSCT) within 100 days before *Nocardia* diagnosis. Immunosuppressant use was assessed in the 28 days prior to *Nocardia* diagnosis, and corticosteroid dosing was the most recent recorded dose in the past 28 days, converted to equivalent dosing of prednisone. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis was assessed on the date of initial presentation. Active malignancy included radiographic or laboratory evidence of malignancy or receiving antineoplastic chemotherapy within 28 days of diagnosis. Laboratory values were assessed on the date of diagnosis or the most recent prior measurement. CNS symptoms included documentation of headache, confusion, paresthesia, or focal weakness. Combination therapy was defined as receipt of at least 2 initial antibiotic agents. Active antibiotic agents were those that were initially used and later tested susceptible.

Statistical Analysis

Continuous variables were summarized as median (IQR) and categorical variables as number (percentage). The primary outcome was 1-year mortality after diagnosis of nocardiosis. Patients without mortality were censored at last follow-up or 1 year postdiagnosis, whichever occurred first. Kaplan-Meier curves were constructed to illustrate differences in cumulative incidence of mortality after diagnosis between groups. Differences in between-group survival were tested by the log-rank test. Cox proportional hazards regression was then used to analyze associations with the primary outcome. Variables of interest were first analyzed in univariable analyses, followed

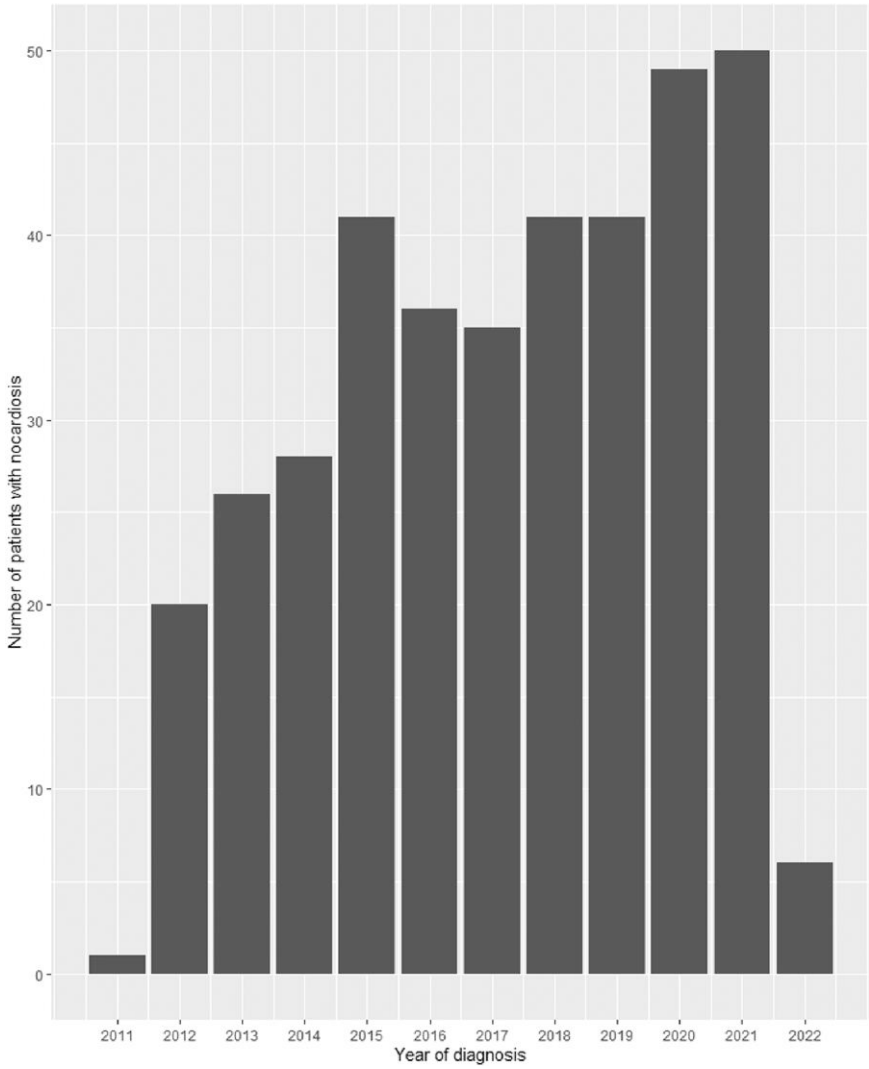

Figure 1. Number of patients with nocardiosis by year of diagnosis. Note that 2011 included only November and December while 2022 included only January through April.

by multivariable analyses. Two multivariable models were constructed to test disseminated and advanced infection separately, incorporating the same adjuster variables. Adjuster variables were described associations in past studies or suspected confounders with mortality. Adjuster variables and advanced infection were both defined a priori. Additionally, all Cox models were stratified by treatment center. Given that pulmonary cavitation is a subset of pulmonary nocardiosis, the main analyses were repeated in the subgroup of patients with pulmonary involvement. Isolates that were unable to be identified to the species level were assumed to not be *N. farcinica*, as the standard identification methods should reliably identify this species [15, 16, 19, 20]. Sensitivity analyses were performed excluding isolates with unidentified species to assess this assumption. Given the possibility of *Nocardia* respiratory colonization being misclassified as true nocardiosis among patients with chronic lung disease who were immunocompetent, a sensitivity analysis was performed excluding these patients. Finally, a sensitivity analysis was performed excluding those without CNS imaging to account for the possibility of unrecognized disseminated infection. The proportional hazards assumption was assessed by Schoenfeld residuals. All analyses were performed with R version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

Initially, 511 patients were identified with culture growth of *Nocardia*. After the exclusion of 137 (26.8%) determined to be colonized without clinical disease, 374 patients with nocardiosis were included in this study. The highest proportion were diagnosed at the center in Arizona (n = 162, 43.3%), followed by Minnesota (n = 124, 33.2%) and Florida (n = 88, 23.5%). The number of nocardiosis cases appeared to increase over

the study period (Figure 1). The median age was 65.3 years (IQR, 51.0–72.6), and a majority were male (n = 210, 56.1%). An overall 117 (31.3%) were recipients of solid organ transplantation (Supplementary Table 1); 38 (10.2%) had previously received an HSCT; and 43 (11.5%) had evidence of active malignancy at diagnosis. The median time from solid organ transplantation to diagnosis was 484.0 days (IQR, 204.0–1636.0), and that for recipients of HSCT was 524.5 days (IQR, 190.0–1836.0). HSCTs included 28 allogeneic and 10 autologous transplants. Only 1 recipient of autologous HSCT did not meet criteria for immunocompromised status. In total 213 (57.0%) patients had received an immunosuppressant medication within 28 days of diagnosis. The most common medication was corticosteroids (n = 178, 47.6%). The median daily prednisone equivalent dose was 10.0 mg (IQR, 5.0–17.0). Thirteen patients receiving corticosteroids did not meet criteria for immunocompromised status (daily prednisone equivalent dose range, 5.0–17.5 mg). No patients were living with HIV. Additional baseline characteristics are shown in Table 1.

Seventy-four patients (19.7%) had disseminated infection at diagnosis. Among patients with localized infection, the most common sites of involvement were the lungs (n = 243, 81.3%) and skin (n = 42, 14.0%). Of patients with disseminated infection, 53 (71.6%) had CNS involvement and 14 (18.9%) were bacteremic (Table 2). Mutually exclusive specific sites of infection are detailed in Supplementary Table 2. The most common *Nocardia* species isolated were *N cyriacigeorgica* (n = 81, 21.7%) and *N farcinica* (n = 80, 21.4%). Ten (2.7%) isolates' species were unidentified (Supplementary Figure 1). Antimicrobial susceptibility results were available for 366 (97.9%) isolates (Supplementary Table 3). Isolates were universally susceptible to linezolid (n = 366, 100%), and nearly all were susceptible to TMP-SMX (n = 350, 95.6%) and amikacin (n = 331, 90.4%).

Patients with chronic pulmonary disease who were not immunocompromised represented 27.8% of the total cohort. Only 2 (1.9%) had disseminated infection, both with cavitary pulmonary infection and involvement of either the CNS or skin.

Nondisseminated cases included 1 each with pleural involvement and vocal cord involvement, while the remaining 100 featured localized pulmonary infection. Of these 100 with localized pulmonary infection, 6 had lung cavitation.

Patients infected with *N farcinica* had a higher rate of CNS imaging (78.8% vs 68.0%) and received a comparable number of initial antibiotics (median [IQR], 2.0 [1.0–3.0] vs 2.0 [1.0–2.0]) and active antibiotics (1.0 [1.0–2.0] for both groups). Initial antibiotic use was similar between those with *N. farcinica* and non–*N. farcinica* species, with slightly higher rates of amoxicillin-clavulanate, imipenem, linezolid, moxifloxacin, and meropenem usage and a lower rate of ceftriaxone usage (6.2% vs 10.5%).

Presenting Characteristics

A total of 226 (60.4%) patients were hospitalized for nocardiosis, with 36 (9.6%) being admitted or transferred to the intensive care unit. Nineteen (5.1%) required invasive mechanical ventilation, and 14 (3.7%) required vasopressor support for shock. The median hospital length of stay was 7.0 days (IQR, 4.0–14.0), which was longer for those with disseminated infection (12.0 vs 6.0 days). The median time from symptom onset to diagnosis was 17.0 days (IQR, 7.0–63.2), which was shorter in patients with disseminated infection. The most common presenting symptoms were cough (n = 224, 59.9%), malaise (n = 147, 39.3%), dyspnea (n = 143, 38.2%), and fever (n = 94, 25.1%). Forty-two (11.2%) had documented CNS symptoms, such as headache (n = 21, 5.6%), confusion (n = 16, 4.3%), focal weakness (n = 14, 3.7%), and paresthesia (n = 6, 1.6%). Of 309 (82.6%) patients with pulmonary involvement, 297 (96.1%) underwent computed tomography of the chest. This showed that 50 (16.8%) had cavitary infection and 220 (74.1%) had pulmonary nodules. Additional presenting and treatment characteristics are included in Table 3. Forty-six (12.3%) were receiving TMP-SMX primary prophylaxis at diagnosis. The most common initial antibiotic agent for treatment was TMP-SMX (n = 283, 75.7%), and 207 (55.3%) initially received combination therapy. Frequencies of all initial antibiotic agents as well as TMP-SMX primary prophylaxis dosing are presented in Supplementary Table 4. Patients who completed treatment received a median 190.0 days (IQR, 102.0–299.5) of therapy. This was twice as long for those with disseminated infection (median, 365.0 days) vs localized infection (182.0 days).

An overall 117 (31.3%) patients met criteria for advanced infection. These nonmutually exclusive categories included 74 (63.2%) with disseminated infection, 50 (42.7%) with cavitary pulmonary infection, and 18 (15.4%) with pleural involvement. Among those with pleural involvement, pleural cultures were collected on the date of first positive culture ascertainment in all but 2 patients (range, 0–2 days). Characteristics of those with and without advanced infection are summarized in Supplementary Table 5.

Risk Factors for Mortality

In total, 59 patients (16.2% by inversed Kaplan-Meier estimation) died within 1 year of diagnosis (Supplementary Figure 2). Median time to death was 109.0 days (IQR, 26.5–258.5). Of the remaining patients, all but 37 had complete 1-year follow-up. These 37 had a median follow-up of 287.0 days (IQR, 154.0–322.0). Kaplan-Meier curves of survival by site of infection are shown in Supplementary Figure 3. Patients with disseminated infection, cavitary pulmonary infection, pleural infection, and advanced infection had lower 1-year survival (Figure 2). Patients who had a Charlson Comorbidity Index (CCI) ≥5, immunocompromised status, and *N farcinica*

Table 1. Baseline Characteristics of 374 Patients With Nocardiosis

	Nondisseminated (n = 300)	Disseminated (n = 74)	Total (N = 374)
Age, y	65.4 (56.9–73.6)	63.9 (57.6–69.6)	65.3 (57.0–72.6)
Male sex	162 (54.0)	48 (64.9)	210 (56.1)
Race			
American Indian or Alaska Native	5 (1.7)	2 (2.7)	7 (1.9)
Asian	9 (3.0)	1 (1.4)	10 (2.7)
Black or African American	11 (3.7)	5 (6.8)	16 (4.3)
Native Hawaiian or other Pacific Islander	1 (0.3)	0 (0.0)	1 (0.3)
White	271 (90.7)	66 (89.2)	338 (90.4)
Other	1 (0.3)	0 (0.0)	1 (0.3)
Unknown	1 (0.3)	0 (0.0)	1 (0.3)
Ethnicity			
Hispanic or Latino	18 (6.0)	3 (4.1)	21 (5.6)
Not Hispanic or Latino	281 (93.7)	70 (94.6)	351 (93.9)
Unknown	1 (0.3)	1 (1.4)	2 (0.5)
Charlson Comorbidity Index	2.0 (1.0–3.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)
Chronic pulmonary disease	144 (48.0)	12 (16.2)	156 (41.7)
Bronchiectasis	82 (56.9)	1 (8.3)	83 (53.2)
COPD	34 (23.6)	8 (66.7)	42 (26.9)
Cystic fibrosis	2 (1.4)	0 (0.0)	2 (1.3)
Interstitial lung disease	21 (14.6)	3 (25.0)	24 (15.4)
Other[a]	5 (3.5)	0 (0.0)	5 (3.2)
Diabetes mellitus	62 (20.7)	22 (29.7)	84 (22.5)
Chronic kidney disease[b]	100 (33.3)	36 (48.6)	136 (36.4)
Chronic hemodialysis	5 (1.7)	2 (2.7)	7 (1.9)
Immunocompromised status	142 (47.3)	58 (78.4)	200 (53.5)
Solid organ transplant	81 (27.0)	36 (48.6)	117 (31.3)
Hematopoietic stem cell transplant	32 (10.7)	6 (8.1)	38 (10.2)
Active malignancy	35 (11.7)	8 (10.8)	43 (11.5)
Immunosuppressant use	152 (50.7)	61 (82.4)	213 (57.0)
Corticosteroid	126 (42.0)	52 (70.3)	178 (47.6)
Tacrolimus	89 (29.7)	37 (50.0)	126 (33.7)
Mycophenolate	65 (21.7)	32 (42.2)	97 (25.9)
Chemotherapy	15 (5.0)	5 (6.8)	20 (5.3)
Azathioprine	6 (2.0)	2 (2.7)	8 (2.1)
Cyclosporine	6 (2.0)	2 (2.7)	8 (2.1)
Ruxolitinib	6 (2.0)	2 (2.7)	8 (2.1)
Anti-CD20 antibody	5 (1.7)	3 (4.1)	8 (2.1)
Methotrexate	6 (2.0)	1 (1.4)	7 (1.9)
TNF-α inhibitor	4 (1.3)	2 (2.7)	6 (1.6)
Other immunosuppression[c]	7 (2.3)	4 (5.4)	11 (2.9)
Immunocompetent			
With chronic lung disease	102 (34.0)	2 (2.7)	104 (27.8)
Without chronic lung disease	56 (18.7)	14 (18.9)	70 (18.7)
TMP-SMX primary prophylaxis	35 (11.7)	11 (14.9)	46 (12.3)
N farcinica	53 (17.7)	27 (36.5)	80 (21.4)
Advanced infection	43 (14.3)	74 (100.0)	117 (31.3)
Count, $\times 10^9$/L			
Leukocyte (n = 370)	8.1 (5.8–10.4)	9.2 (5.8–14.0)	8.2 (5.7–10.9)
Lymphocyte (n = 361)	1.1 (0.5–1.7)	0.6 (0.3–1.0)	1.0 (0.5–1.6)
Neutrophil (n = 361)	5.4 (3.6–7.9)	7.2 (3.9–12.6)	5.6 (3.6–8.4)

Data are No. (%) or median (IQR).

Abbreviations: COPD, chronic obstructive pulmonary disease; TMP-SMX, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor.

[a]Other chronic pulmonary diseases include asthma (n = 3), Mounier-Kuhn syndrome (n = 1), and chronic tracheal stenosis (n = 1).

[b]Chronic kidney disease was defined as a baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2, as calculated by the 2021 CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration).

[c]Other immunosuppression includes ibrutinib (n = 3), acalabrutinib (n = 2), sirolimus (n = 3), belatacept (n = 2), and leflunomide (n = 1).

had significantly higher 1-year mortality (Supplementary Figures 4–6). Patients with advanced infection without dissemination had lower survival than patients with disseminated infection and nonadvanced infection (Supplementary Figure 7). Patient survival stratified by advanced infection categorization is shown in Supplementary Figure 8.

Table 2. Sites of *Nocardia* Infection

	Nondisseminated (n = 300)	Disseminated (n = 74)	Total (N = 374)
Lungs	243 (81.0)	66 (89.2)	309 (82.6)
Pleura	14 (4.7)	4 (5.4)	18 (4.8)
Skin	42 (14.0)	25 (33.8)	67 (17.9)
CNS	0 (0.0)	53 (71.6)	53 (14.2)
Blood	1 (0.3)	14 (18.9)	15 (4.0)
Lymph node	1 (0.3)	4 (5.4)	5 (1.3)
Joint	3 (1.0)	2 (2.7)	5 (1.3)
Bone	3 (1.0)	1 (1.4)	4 (1.1)
Endocarditis	0 (0.0)	1 (1.4)	1 (0.3)
Other	6 (2.0)[a]	15 (20.3)[b]	21 (5.6)

Data are No. (%). These sites are not mutually exclusive, and the column sum may exceed 100%. The only overlap in the nondisseminated group is that some patients with lung involvement may have also had pleural involvement.

Abbreviation: CNS, central nervous system.

[a]Other localized sites included tenosynovitis (n = 2), keratitis, sinusitis, thyroiditis, and vocal cords.

[b]Other disseminated sites included muscle abscess (n = 3), pelvic abscess (n = 3), bone marrow (n = 2), choroiditis, intra-abdominal abscess, liver, perinephric abscess, peritonitis, subglottic mass, and thrombophlebitis.

In unadjusted analysis, disseminated infection, cavitary pulmonary infection, pleural infection, advanced infection, higher CCI, immunocompromised status, and initial combination therapy were associated with 1-year mortality while age was not (Table 4). In adjusted analysis, disseminated infection was not associated with 1-year mortality (hazard ratio [HR] 1.16; 95% CI, .62–2.16; $P = .650$). Those with cavitary pulmonary infection had a higher, though nonsignificant, risk of 1-year mortality (HR, 1.65; 95% CI, .89–3.05; $P = .111$), and pleural involvement was associated with increased risk of mortality (HR, 4.60; 95% CI, 2.14–9.89; $P < .001$). Advanced infection (a composite of dissemination, lung cavitation, and pleural infection) was significantly associated with 1-year mortality (HR, 2.48; 95% CI, 1.37–4.49; $P = .003$) after adjusting for the same factors. In this analysis, a higher CCI and infection with *N. farcinica* were associated with 1-year mortality while immunocompromised status, combination therapy, and age were not significant. The effect measures were similar among the subgroups with pulmonary infection, though the HR of pleural involvement was somewhat attenuated but still statistically significant (Supplementary Table 6). The results were similar in sensitivity analyses excluding patients who were immunocompetent with chronic pulmonary disease and an analysis excluding those without CNS imaging. To assess if its effect was primarily driven by those with pleural involvement, the adjusted analysis of advanced infection was repeated after excluding the 18 patients with pleural infection. This showed a similar, though

Table 3. Presenting and Treatment Characteristics

	Nondisseminated (n = 300)	Disseminated (n = 74)	Total (N = 374)
Time from symptom onset to diagnosis, d	19.0 (7.0–76.5)	10.0 (7.0–28.5)	17.0 (7.0–63.2)
CNS symptoms	13 (4.3)	29 (39.2)	42 (11.2)
Brain imaging	189 (63.0)	74 (100.0)	263 (70.3)
Head CT	102 (34.3)	41 (54.1)	143 (38.2)
Brain MRI	125 (42.0)	69 (91.9)	194 (51.9)
Chest CT	255 (85.0)	70 (94.6)	325 (86.9)
Hospitalization	154 (51.3)	72 (97.3)	226 (60.4)
ICU admission	19 (6.3)	17 (23.0)	36 (9.6)
Procedural intervention	37 (12.3)	29 (39.2)	66 (17.6)
Neurosurgery	0 (0.0)	14 (18.9)	14 (3.7)
Thoracic surgery	6 (2.0)	4 (5.4)	10 (2.7)
Orthopedic surgery	6 (2.0)	2 (2.7)	8 (2.1)
Soft tissue debridement	22 (7.3)	7 (9.5)	29 (7.8)
Other	5 (1.7)	2 (2.7)	7 (1.9)
Time from culture ascertainment to treatment start, d	7.0 (1.0–20.0)	3.0 (1.0–5.0)	5.0 (1.0–17.0)
Initial combination therapy	138 (46.0)	69 (93.2)	207 (55.3)
No. of initial agents	1.0 (1.0–2.0)	2.0 (2.0–3.0)	2.0 (1.0–2.0)
No. of active initial agents (n = 366)[a]	1.0 (1.0–2.0)	2.0 (2.0–2.0)	1.0 (1.0–2.0)
Length of therapy (n = 310)[b]	182.0 (92.5–247.5)	365.0 (207.5–428.5)	190.0 (102.0–299.5)
Secondary prophylaxis (n = 310)[b]	53 (20.5)	21 (41.2)	74 (23.9)

Data are No. (%) or median (IQR).

Abbreviations: CNS, central nervous system; CT, computed tomography; ICU, intensive care unit; MRI, magnetic resonance imaging.

[a]Excluding patients without available antimicrobial susceptibility testing results.

[b]Excluding patients who either died prior to completing therapy or had not yet completed therapy.

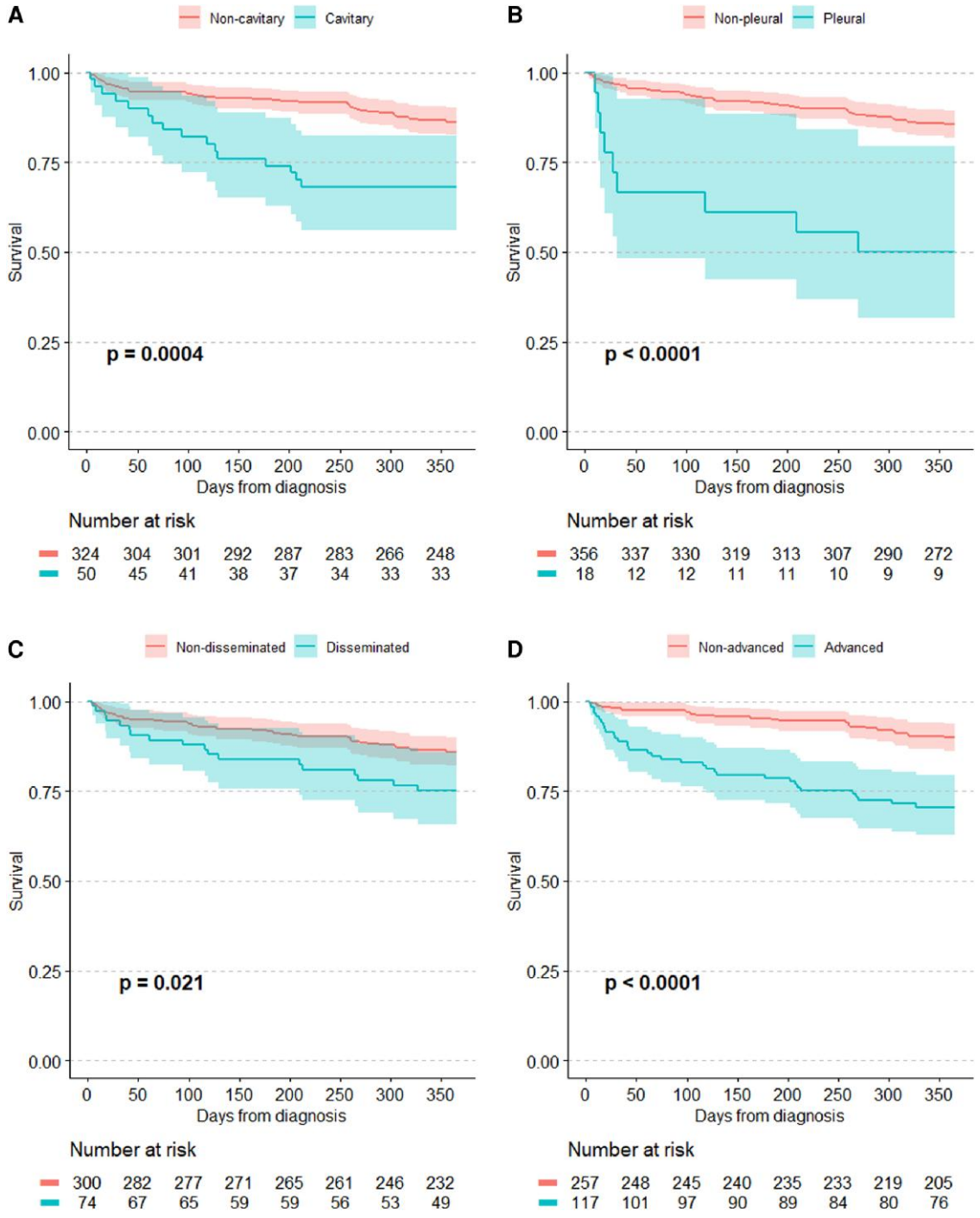

Figure 2. Kaplan-Meier curves comparing 1-year survival among all 374 patients with nocardiosis based on (*A*) cavitary pulmonary infection, (*B*) pleural infection, (*C*) disseminated infection, and (*D*) advanced infection. *P* values are calculated via the log-rank test. Shading indicates 95% CI.

slightly attenuated, increased risk of mortality (HR, 2.18; 95% CI, 1.15–4.17; $P = .018$).

DISCUSSION

We performed a retrospective cohort study analyzing risk factors for mortality following *Nocardia* infection. While disseminated infection was associated with mortality in univariable analysis, this factor was not significant after adjusting for potential confounders. Furthermore, advanced infection—defined as dissemination, pleural involvement, or cavitary pulmonary infection—was associated with higher mortality after incorporating the same adjusters. Additionally, a higher

Table 4. Risk Factors for Mortality After Diagnosis of Nocardiosis

	Univariable Analysis		Multivariable Analysis 1		Multivariable Analysis 2	
Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Disseminated infection	1.91 (1.10–3.22)	**.022**	1.16 (.62–2.16)	.650	…	
Pulmonary cavitation	2.71 (1.52–4.81)	**<.001**	1.65 (.89–3.05)	.111	…	
Pleural involvement	5.34 (2.26–11.14)	**<.001**	4.60 (2.14–9.89)	**<.001**	…	
Advanced infection	3.44 (2.05–5.78)	**<.001**	…		2.48 (1.37–4.48)	**.003**
CCI per 1 point	1.40 (1.24–1.59)	**<.001**	1.38 (1.19–1.59)	**<.001**	1.38 (1.19–1.59)	**<.001**
Immunocompromised status	2.49 (1.38–4.48)	**.002**	1.38 (.73–2.61)	.329	1.17 (.61–2.22)	.642
N. farcinica	1.98 (1.14–3.43)[a]	**.015**	2.35 (1.30–4.24)[b]	**.005**	2.09 (1.17–3.72)[c]	**.013**
Initial combination therapy	2.05 (1.16–3.60)	**.013**	1.08 (.55–2.10)	.832	0.93 (.48–1.82)	.834
Age per 1 y	1.00 (.98–1.02)	.998	1.00 (.98–1.02)	.903	1.00 (.98–1.02)	.819

Bold values indicate $P < .05$.

Abbreviations: CCI, Charlson comorbidity index; HR, hazard ratio.

[a]After exclusion of patients with unidentified *Nocardia* species: HR, 1.91; 95% CI, 1.10–3.31; $P = .021$.

[b]After exclusion of patients with unidentified *Nocardia* species: HR, 2.30; 95% CI, 1.28–4.13; $P = .005$.

[c]After exclusion of patients with unidentified *Nocardia* species: HR, 2.04; 95% CI, 1.14–3.62; $P = .016$.

burden of comorbidities and infection with *N farcinica* were associated with poor outcomes.

The discordance between outcomes from disseminated and advanced infection may be explained by heterogeneity in infection severity among patients with localized infection. Patients with disseminated infection have a rate of crude mortality as high as 36.8% [5, 9], while those with primary cutaneous or other uncommon localized sites rarely experience poor outcomes, with 1-year mortality as low as 2.2% [1, 21, 22]. However, pulmonary nocardiosis accounts for most localized infections, and infection severity likely varies significantly among patients, resulting in varied outcomes in reported literature. Mortality rates of pulmonary nocardiosis have varied among studies, typically about 16% to 25%, but studies with the highest proportions of cavitary infection often have higher overall crude mortality [23–25]. This variability also seems to correspond with underlying immune status, where patients with immunocompromise and pulmonary nocardiosis are more likely to present with cavitary infection [26]. Yet, after controlling for immunocompromised status, our analysis found that incorporating high-risk presenting characteristics—namely, cavitary pulmonary infection or pleural involvement—with disseminated infection improved prognostic capacity for mortality.

There is precedence for similar criteria in other localized pulmonary infections, such as pulmonary mycobacterial infection, where cavitation is incorporated as a marker of severe or advanced disease [27, 28]. In these infectious syndromes, cavitation has been associated with higher microbiologic burden [29, 30], disease progression [30–32], treatment failure [33], and mortality [31, 32, 34]. Similarly, pleural infections are associated with high mortality overall [35], which has been demonstrated in nocardiosis specifically [10].

The improved prognostication from advanced infection is not meant to discount the utility of disseminated infection as a clinical term. It remains important to evaluate for distant sites of infection from those that are clinically apparent. Discovery of specific sites, such as CNS infection, may require changes in therapy for adequate tissue penetration, as well as procedural interventions [36, 37]. However, dissemination alone may not fully convey an individual patient's risk for poor outcomes.

Another observation worth noting is the relative rarity of patients with chronic pulmonary disease to develop either disseminated or advanced infection. Among those with bronchiectasis, only 1.2% and 4.8% developed disseminated and advanced infection, respectively. T lymphocytes have been shown to be vital in the immune response to nocardiosis [38], and quantitative or qualitative cellular immune deficits may account for the differences in presentation between those who are immunocompromised and immunocompetent with chronic lung disease whose primary predisposing factor is localized structural abnormalities. Nocardiosis in the population with chronic lung disease may more closely resemble infection with nontuberculous mycobacteria, another infection that is common among this group but associated with relatively low mortality overall [31, 32].

These data also highlight the high-risk nature of *N farcinica* as an invasive *Nocardia* species. Past data have shown *N farcinica* to be associated with disseminated infection [9], though ours is the first study to associate this species with mortality. Interestingly, higher risk of mortality persisted despite adjusting for either disseminated or advanced infection, suggesting that *N farcinica* may have intrinsic characteristics that predispose to more aggressive infection and worse outcomes [39].

A higher burden of comorbidities, as measured by the CCI, is associated with mortality after nocardiosis. This is consistent with prior analyses, where comorbidities or lack of malignancy remission was associated with mortality [5, 40]. However, though significant in unadjusted analysis, we did not find immunocompromised status to be associated with mortality in our multivariable analysis. It is more likely that patients who are immunocompromised are at

higher risk for more invasive or advanced infection [9, 26], though outcomes after development of nocardiosis are more reliant on infection severity than underlying immune status.

These findings have several possible implications for *Nocardia* therapy. Nocardiosis guidelines and expert opinions often cite longer durations of therapy or use of combination therapy for patients who are immunocompromised [7]; however, our data suggest that infection severity affects outcomes rather than immune status. This is in line with emerging data suggesting that courses <120 days may be adequate for populations that are immunocompromised, such as recipients of solid organ transplantation [11, 41]. Specific sites or severity of infection may better direct therapeutic decision making, including the need for combination antimicrobial therapy and optimal duration of therapy. Future studies should account for advanced infection when analyzing patients with nocardiosis and antimicrobial therapy.

This analysis has several limitations worth noting. First, it was conducted retrospectively and is subject to potential sources of bias and confounding that are difficult to fully eradicate. Second, the definition of advanced infection was based on objective data that are readily accessible retrospectively. Some markers of more severe infection were unable to be reliably assessed, and the criteria for advanced infection may need to be validated and revised in future studies. Third, there were some missing data, such as species identification and laboratory values (eg, lymphocyte counts), which have been associated with disseminated infection [9]. While we performed sensitivity analyses to account for missing *Nocardia* species, we were unable to incorporate some other factors. Fourth, not all patients had CNS imaging, resulting in some cases possibly being misclassified as nondisseminated or nonadvanced based on the clinical data available. Fifth, patients likely received different management strategies, such as initial combination therapy, based on perceived risk, and this may have influenced outcomes. Finally, some patients likely died from causes independent from nocardiosis, though all-cause mortality was analyzed to avoid the subjectivity of assigning an attributable cause of death. Additionally, downstream effects of severe infection or antimicrobial toxicity, such as renal dysfunction, may have contributed to mortality that was not directly infection related.

In conclusion, this study found that disseminated infection alone does not independently predict mortality after nocardiosis. Instead, a novel definition for advanced infection may perform better in predicting outcomes from *Nocardia*. Additional risk factors for mortality were found, including a higher burden of comorbidities and infection with *N farcinica*, while immunocompromised status and up-front combination antibiotic therapy were not significant in adjusted analysis. Future studies of nocardiosis should account for the specific sites and severity of infection rather than simply the presence of dissemination.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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