Meta-Analysis of Observational Studies in Epidemiology

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Scedosporium spp lung infection in immunocompetent patients

A systematic review and MOOSE-compliant meta-analysis

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Abstract

Scedosporium genus as a significant emerging opportunist causes a broad spectrum of disease in not only immunosuppressed but also immunocompetent patients. The lung is one of the most commonly encountered sites of *Scedosporium* infection. Due to its very high levels of antifungal resistance, surgery has been recommended as an important part in the treatment of pulmonary *Scedosporium* spp infection, even in immunocompetent cases. However, whether lung surgery could help to reduce the risk of death in immunocompetent patients is not clear.

We retrospectively retrieved the records of pulmonary infections with *Scedosporium* species in immunocompetent patients through a comprehensive literature search. The association of surgery on all-cause mortality was explored using binary logistic regression (BLR). Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the capability of the model.

The comprehensive searching strategy yielded 33 case reports and 3 case series in total, with 40 individual patients being included. The overall mortality was 12.50%. The fatality rate was 9.09% (2/22) in cases with surgery and 16.67% (3/18) in cases without surgery (odds ratio, 0.50; 95% confidence interval, 0.07–3.38; $P = .48$). Consistently, BLR analysis identified no statistical association between surgery and reduced mortality (odds ratio, 1.19; 95% confidence interval, 0.09–15.64; $P = .89$), after adjusting for age, gender, and antifungal chemotherapy. The area under the ROC curve was 0.88.

For immunocompetent patients with pulmonary *Scedosporium* spp infection, surgical therapy may not be associated with reduced mortality. Surgical excision could be considered but is not imperative in this group of patient.

Abbreviations: BAL = bronchoalveolar lavage, ROC = receiver operating characteristic.

Keywords: lung infection, mortality, *Scedosporium* spp, surgery, systematic review

1. Introduction

The genus *Scedosporium* comprises a group of filamentous fungi found ubiquitously in soil, sewage, and polluted waters. Recent advances in molecular taxonomy have demonstrated a complex of at least 10 distinct species for *Scedosporium* genus, with 5 of them causing human infections, namely *Scedosporium apiospermum* (*S apiospermum*) (formerly *Monosporium apiospermum*), *Pseudallescheria boydii* (*P boydii*) (formerly *Allescheria boydii* and *Petriellidium boydii*, the teleomorph of *S apiospermum*), *S minutispora*, *S dehoogii*, and *S aurantiacum*.[1,2]

As opportunistic pathogens, infections caused by *Scedosporium* spp are largely associated with compromised immune status.[3] However, *Scedosporium* spp have also been reported in immunocompetent hosts, although classically related with traumas, near-drowning incidence, or tsunami.[4] *Scedosporium* spp are increasingly recognized as causes of a wide spectrum of life-threatening infections affecting a lot of sites including skin, lung, soft tissue, central nerve system, and sinuses.[5,6] Among them, pulmonary infection ranked 2nd. Although usually attack patients with underlying pulmonary disorders,[7] *Scedosporium* spp also affect otherwise healthy patients.[8]

Scedosporium spp pose a great therapeutic challenge due to their intrinsic resistance to traditional antifungal agents and their tendency to relapse, despite demonstrating susceptibility to the treatment.[9,10] Surgery is commonly considered in *Scedosporium* spp pulmonary infections whenever the lesions are resectable, even among immunocompetent patients.[4] Studies have suggested that surgical excision may favor the patient's overall chance for survival. However, the critical role of surgery is disputed and may have to be comprehensively reviewed in the light of the emerging of new antifungal agents that target the fungus more precisely.

We comprehensively summarize cases of pulmonary *Scedosporium* spp infections in immunocompetent patients from

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published literatures. We aim to evaluate the place of surgical excision in this group of patients and provide evidence for effective therapy to combat these organisms.

2. Methods

This systematic review and meta-analysis was conducted and reported according to the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE).[11] The ethical approval and patient consent were not necessary for our study as this was a literature review based on published data and would not involve direct contact with patients or alterations to patient care.

2.1. Eligibility criteria

Published case reports/series of localized *Scedosporium* spp lung infection in immunocompetent patients ≥18 years old were reviewed. Patient outcome must be adequately reported. All cases should have positive etiological culture or macroscopic observation. *Lomentospora prolificans* was also investigated although it was reclassified to *Lomentospora* genus in 2014,[12] as it had been considered as one of the genus *Scedosporium* since 1991 (called *S prolificans* or *S inflatum*) due to their phylogenetical relation.[4] Lung should be the primary site of the infection. Cases with disseminated infections with *Scedosporium* spp isolated from 2 or more noncontiguous sites showing clinical or histological evidence of infection would be excluded. Reviews, abstracts, and poorly documented cases with absence of primary individual information were excluded. Cases with possible or proven immunosuppressive conditions, such as carcinoma, hematological malignancy, organ transplantation, acquired immune deficiency syndrome, diabetes, and long-term (at least 1 month) use of oral or systematic corticosteroid, antibiotic, or immunosuppressant, were excluded. We also excluded cases suffering near-drowning, tsunami/earthquake or chest trauma.

2.2. Search strategies and data extraction

A systematic search using keywords and MeSH of "pulmonary," "lung," "scedosporiosis," "scedosporium," "scedosporiums," "scedosporium prolificans," "scedosporium prolifican," "scedosporium apiospermum," "scedosporium boydii," "pseudallescheria boydii," "monosporiums," "monosporium apiospermum," "pseudallescheria," "pseudallescherias," "allescheria," "allescherias," "petriellidium," "petriellidiums," "case report," "case series," "immunocompetent" was carried out in PubMed/MEDLINE and Ovid/EMBASE from inception to March 2019 (see Supplementary Digital Content 1, http://links.lww.com/MD/D282, which illustrated the example of search strategy in PubMed/MEDLINE). Reference lists of relevant reports were also searched. The search results were imported in Endnote X7 literature management software. After removal of duplicates, the titles and abstracts were assessed for inclusion. Full texts of relevant articles were retrieved. The reasons for exclusion were recorded. Country of origin, year of publication, age, gender, pathogenic species, initial clinical manifestations, time to diagnosis, underlying conditions, antifungal chemotherapy, treatment duration, use of surgical treatment, follow-up duration, and patient outcome were recorded. Missed information would be collected by contacting with the authors. Article inclusion and data extraction were conducted independently by 2 authors (WL and RZF). Discrepancies over case inclusion and data extraction were resolved by consensus.

2.3. Methodological quality evaluation

We applied an adapted quality assessment scale for noncomparative case reports and case series. This scale comprised 5 items to address 4 domains of potential risk of bias[13]: selection, ascertainment, causality, and reporting (see Supplementary Digital Content 2, http://links.lww.com/MD/D282, which demonstrated the adapted methodological quality tool for noncomparative case reports and case series). Each of the items required a binary response ("Yes" or "No") to indicate whether the bias was likely. We considered the quality of the inclusion good when all 5 criteria were fulfilled, moderate when 4 were fulfilled, and poor when 3 or less were fulfilled. Two authors (WL and RZF) assessed the methodological quality of included case reports or case series with discussion in case of disagreement. We considered studies without follow-up reporting or with a follow-up duration shorter than 12 months were biased in the domain of causality.

2.4. Statistical analysis

Patient demographics, country of origin, pathogenic species, initial clinical manifestations, time to diagnosis, underlying conditions, antifungal chemotherapy, treatment duration, use of surgical treatment, follow-up duration, and patient outcome were summarized descriptively. We examined the effect of surgery on patients' mortality using binary logistic regression. The covariates were age, gender, and antifungal chemotherapy. The strength of the model was then tested by the area under the receiver operating characteristic (ROC) curve. A P value $\leq .05$ was considered to be statistically significant. Statistical analysis was conducted using SPSS v.23.0 (IBM Corp., Armonk, NY).

3. Results

The comprehensive search strategy identified 222 records from the database search. No records were retrieved using hand search from reference lists of all related articles. After removal of duplications, 210 results remained for initial screening. From these, 137 records were excluded because their titles or abstracts were not related to the theme of this review. From the remaining 73 records, 37 were excluded after the full-text assessment because of unexpected patients or reportings (Fig. 1). For cases without reporting outcomes or enough details for assessment, we tried to communicate with authors through their email address to access the data, but no response was received. Finally, 33 case reports and 3 case series with 40 individual patients were included in the final analysis (Fig. 1).

The methodological quality was graded as good, moderate, and poor in 11, 18, and 7 reports, respectively (see Supplementary Digital Content 3, http://links.lww.com/MD/D282, which showed the result of quality assessment for included reports). In all cases, exposure to related pathogens was pathologically confirmed and the patient's outcome was clinically recorded rather than self-reported. Therefore, we considered that all reports had a low risk of bias regarding exposure/outcome ascertainment. The main reasons resulting in a lower quality grade were possible bias in the domains of selection, causality, and reporting. For the domain of selection, all reported cases

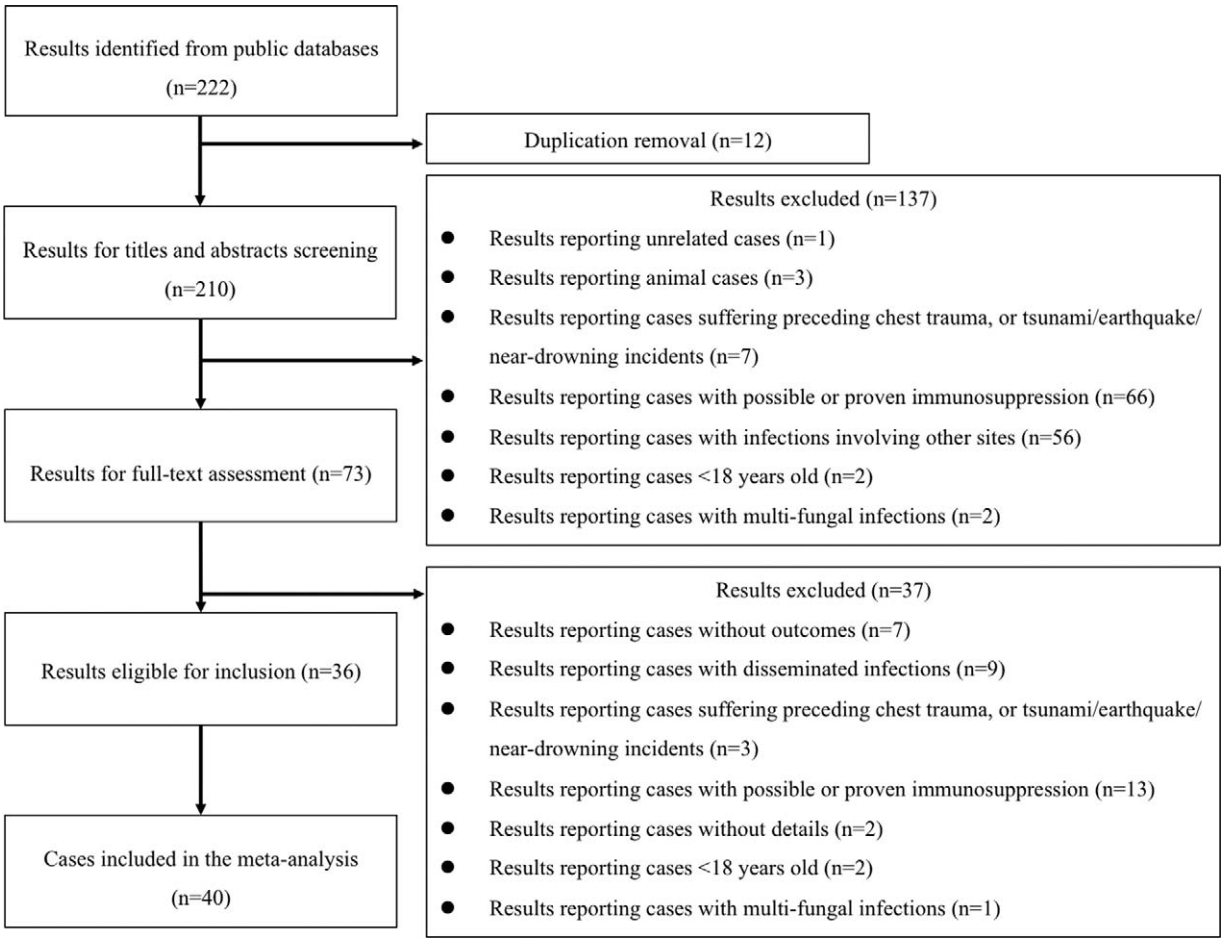

Figure 1. Flow of cases screening and selection.

were demonstrated to be representative. In 3 case series, only 1 explicitly stated that all related cases who presented to the medical center over a certain period were included and reported.[14] For the domain of causality, 14 reports did not describe the conduction of follow-up, 11 reported a follow-up period shorter than 12 months and 1 reported a loss to follow-up.[7] For the domain of reporting, 7 reports failed to show sufficient details about antifungal treatment duration.[7,15–20]

The majority of the cases were from North America (42.5%), followed by Asia (30.0%), Europe (17.5%), and South America (7.5%). The male-to-female ratio was 18:22. Patient's age was 56.4 years (mean) in a range from 26 to 84 years. Characteristics of the included cases were summarized in Table 1.

Cough was the most common presentation (60.0%), followed by hemoptysis or blood-tinged sputum (50.0%) and fever (35.0%). Duration of symptoms ranged from hours to 9 years. The reported time to diagnosis varied from 8 hours to 9 years (median time 5.5 months).[19,21] Previous cavitary damage due to pulmonary tuberculosis was the most common underlying condition (42.5%), followed by bronchiectasis (17.5%). Eleven patients (27.5%) had no obvious predisposing factors for pulmonary *Scedosporium* infection. One patient had cystic fibrosis, but no evidence of immune depression was detected.[22] Imaging examination was done in all cases and showed nonspecific findings. All patients had localized disease. Cavitary lesions and dense opacities were the most common radiological signs, which were reported in 18 and 19 cases, respectively. Fungal ball was found in 3 cases.[19,23,24] Microbiological diagnosis of *Scedosporium* spp was made in all patients based on etiological cultures or morphological findings in bronchoalveolar lavage (BAL) fluid (21 cases), sputum (11 cases), or biopsy tissues (17 cases). For BAL fluid and sputum tests, repeated examinations with negative findings were reported in almost all cases before a final positive result was observed. In 1 case, a positive microbiological result from samples of BAL fluid was available only after the patient's death.[25] The results of lung tissue biopsy were quite consistent. The positive detection rate of *Scedosporium* spp was higher in biopsy samples, compared with that in BAL fluid or sputum samples. Twelve patients had a diagnosis of pulmonary *Scedosporium* infection by postoperative histopathology. In these cases, preoperative testing for fungal detection was not performed or yielded negative results. Antigen testing was positive in 1 patient.[26] *S apiospermum* was the main causative pathogen with a frequency of 57.5%, followed by *P boydii* (37.5%) and *S prolificans* (5.0%). The polymerase chain reaction for species identification was done in 2 patients.[25,27]

Twenty-two infections were managed surgically (52.4%). Operative resection was done either with lobectomy in 13 patients or with wedge resection/segmentectomy in 2 patients.

Table 1

Characteristics of included cases.

Author/year	Age/sex	Country	Causative species	Initial clinical manifestations	Time to diagnosis	Underlying conditions	Antifungal chemotherapy	Treatment duration	Follow-up	Surgery	Outcome
Tong/1958	56/M	USA	*A boydii*	NR	NR	PPT	Stilbamidine	3 mo	NR	Yes	Death
Modesto/1960	26/F	USA	*M apiospermum*	Cough, hemoptysis, pleuritic pain	1 y	None	None		6 wk	Yes	No symptoms
Donald/1966	43/F	USA	*A boydii*	Hemoptysis	6 mo	None	None		16 mo	Yes	Recovery
Reddy/1969*	62/M	USA	*M apiospermum*	Chest pain, cough, blood-streaked sputum	18 mo	PPT; bronchiectasis	None		NR	Yes	Recovery
Reddy/1969*	52/F	USA	*M apiospermum*	Fever, chills, productive cough	6 mo	PPT; bronchiectasis	None		NR	Yes	Recovery
Reddy/1969*	77/F	USA	*M apiospermum*	Cough	NR	None	None		NR	No	Survival
John/1976	56/M	Canada	*P boydii*	Hemoptysis	5 mo	PPT	None		NR	Yes	Recovery
Hanna/1981	32/F	USA	*P boydii*	Fever, productive cough	3 y	None	None		≥2 y	Yes	Recovery
Severo/1982	65/M	Brazil	*P boydii*	Fever, cough, blood tinged sputum	3 mo	APT	None			No	Death
Brett/1982	70/M	UK	*P boydii*	None	NR	None	None		NR	Yes	No recurrence
John/1984†	83/M	USA	*P boydii*	Anorexia, weakness, weight loss	6 wk	None	KE	6 mo	5 mo	No	No recurrence
John/1984†	53/F	USA	*P boydii*	Cough	NR	None	KE	5 mo	20 mo	Yes	No recurrence
John/1984†	70/F	USA	*P boydii*	Productive cough, dyspnea on exertion, fatigue, deceased appetite	1 mo	CRPD	MI, KE	4 mo	11 mo	Yes	No symptoms
Pluss/1985	74/F	USA	*P boydii*	Fever, sweats, cough, pleuritic chest pains	1 y	Lung fibrosis	KE	NR	1 y	No	No symptom, but positive cultures
Jasna/1997	54/F	Croatia	*S apiospermum*	Fever, unproductive cough, dyspnea, weight loss	2 wk	APT	MI, KE	1 y	12 mo	No	No recurrence
Greig/2001	58/F	UK	*S prolificans*	Non-productive cough	5 y	Bronchiectasis	IT	NR	6 mo	Yes	Recovery
Luiz/2004	57/F	Brasil	*S apiospermum*	Thorax pain, hemoptysis	3 mo	PPT	None		1 y	Yes	No recurrence
Gulnaz/2004	32/M	India	*S apiospermum*	Hemoptysis, fever, cough, chest pain	2 wk	PPT	MI	NR	Lost to follow-up	No	Symptom improvement
Takeharu/2005	72/M	Japan	*S apiospermum*	Fever, hemoptysis, growing lung cavity	NR	PPT	MI	1 mo	NR	No	Symptom improvement
Sophie/2007	68/M	France	*S apiospermum*	Dyspnea, hemoptysis, weight loss, asthenia, anorexia, night sweats, pyrexia	6 mo	PPT	VO	1 mo		Yes	Death
Sin-man/2008	53/F	China	*P boydii*	Weight loss, blood-stained sputum	2 mo	Asthma	IT	6 mo	More than 7 mo	No	No recurrence
Sandeep/2010	59/M	USA	*S apiospermum*	Weight loss	1 y	None	VO	3 mo	NR	No	Symptom improvement
Rajeev/2010	27/M	India	*P boydii*	Fever, cough, hemoptysis	3 mo	PPT	IT, OV, AB	10 wk	NR	Yes	Symptom improvement
Ekta/2010	42/M	Ethiopia	*S apiospermum*	Cough, hemoptysis	Few mo	PPT	None		NR	Yes	No recurrence
Gyanshankar/2011	30/F	India	*A boydii*	Cough with expectoration, breathlessness, chest pain, fever	1 y	None	IT	6 mo	4 mo	No	Clinical-radiological improvement
Ryo/2011	71/M	Japan	*S apiospermum*	Cough	9 y	PPT	Liposomal AB+VO, VO	6 mo	1 mo	No	Recovery
Durand/2011	61/F	USA	*S apiospermum*	Cough, dyspnea, hemoptysis	NR	PPT	VO	NR	6 mo	No	Symptom improvement
Kim/2011	72/F	Korea	*S apiospermum*	Productive cough, fever	2 wk	PPT	AB, VO	1 wk		No	Death
Ceccarelli/20122	53/M	India	*S apiospermum*	Fever	10 d	None	Liposomal AB	2 d		No	Death
Gustavo/2012	62/F	USA	*P boydii*	Fever, dyspnea, cough, worsening pulmonary nodules	2 mo	Prior pulmonary MAC infection	VO	NR	NR	No	Clinical-radiological improvement
Gerrahi/2013	40/F	Turkey	*S apiospermum*	Cough, sputum, hemoptysis	5 y	Bronchiectasis	None		5 y	Yes	No complication or recurrence
Agatha/2014	47/M	India	*S apiospermum*	Hemoptysis	3 y	PPT	AB, IT	4 wk	NR	Yes	Recovery
Rodrigo/2015	67/F	Chile	*S apiospermum*	Dyspnea, cough, hemoptysis	1 y	PPT	IT, VO	22 wk	6 mo	No	Clinical-radiological improvement, no recurrence
Carsten/2015	37/F	Germany	*S apiospermum*	Cough, sputum production, dyspnea	1 mo	CF	CA+PO+liposomal AB	6 wk	2 y	No	Clinical-radiological improvement
Nidhi/2015	58/M	USA	*S apiospermum*	Blood tinged sputum	4 d	PPT	VO	NR	NR	No	Symptom improvement
Fasih/2016	40/M	Pakistan	*S apiospermum*	Cough, hemoptysis	4 y	PPT	VO	4 mo	6 mo	Yes	No symptom, radiological improvement
Seiya/2017	68/F	Japan	*S prolificans*	Fever	1 y	Bronchiectasis	VO	10 mo	7 mo	Yes	Survival
Cristina/2017	84/M	Spain	*P boydii*	Hemoptysis	8 h	Prior pleural tuberculosis	VO	NR	18 mo	Yes	No symptom or recurrence
Kevin/2017	51/F	USA	*S apiospermum*	Cough, night sweats	6 wk	None	VO	3 mo	NR	Yes	Recovery
Nana/2018	73/F	Japan	*S apiospermum*	Abnormal chest imaging findings	NR	Lung carcinoid tumorlet	None		5 y	Yes	No recurrence

AB = amphotericin-B, APT = active pulmonary tuberculosis, CA = caspofungin, CF = cystic fibrosis, CRPD = chronic restrictive pulmonary disease, F = female, IT = itraconazole, KE = ketoconazole, M = male, MAC = mycobacterium avium complex, MI = miconazole, NR = not reported, PO = posaconazole, PPT = prior pulmonary tuberculosis, VO = voriconazole.

* Cases from the same case series.

† Cases from the same case series.

Pneumonectomy was done in 2 patients who had diffuse pulmonary infiltrate.[26,28] Combined lobectomy and segmentectomy were performed in 1 patient.[29] Eleven patients received a combination of surgical and antifungal treatment. Among them, 8 patients had a preoperative detection of *Scedosporium* spp and were on antifungal therapy before the surgery. In these cases, surgery was conducted considering persistent or deteriorated symptoms or the possibility of drug resistance. Continuing use of antifungal agents to the postoperative course was performed in 2 patients.[30,31] Two patients had an incidental diagnosis of *Scedosporium* infection following surgery and received postoperative antifungal therapy.[14,24] One patient received an empirical use of antifungal agent before the confirmation of fungal infection after surgery.[23]

Antifungal chemotherapy was performed in 27 cases in total, of which 16 cases used antifungal therapy alone. The use of antifungals before 1982 was rare due to the scarcity of effective medications. One case published in 1958 reported the use of 2-hydroxy-stilbamidine for lung *Scedosporium* infection and the treatment was discontinued due to a severe renal toxicity.[32] Ketoconazole and miconazole were the most frequently used medication before 2005. Voriconazole was considered as the 1st-line medication for *Scedosporium* infection in recent decades. It was prescribed in 12 cases in total and was administrated as the postoperative antifungal treatment in 2 cases.[24,30] Conventional therapies for fungal infections such as amphotericin-B, itraconazole, and posaconazole were randomly used. Most patients were treated with single antimycotics. The most frequent monotherapy was voriconazole (Table 1). Triple therapy with a combined regimen of caspofungin, posaconazole, and liposomal amphotericin-B was adopted in 1 case.[22] In 1 patient, double therapy with combined liposomal amphotericin-B and voriconazole was administrated as the initial treatment but was later changed to a monotherapy of voriconazole in increased dosage for better effect.[21] Twenty cases reported treatment duration of antifungal agents. Chemotherapy lasted from 2 days to 12 months (median 3.0 months). Antifungal minimum inhibitory concentrations were measured in 6 reports.[20,22,24,27,30,33] Four cases reported drug-related side-effect attributed to miconazole and voriconazole, leading to the discontinuation of treatment.[8,22,34,35]

Postoperative course was uneventful in 3 patients.[28,36,37] Recovery was reported in 9 patients, of whom 8 received surgical resection. Sixteen patients (40.0%) responded well to chemotherapy alone with improving clinical and radiological findings. One patient was asymptomatic but chronically colonized with *P boydii* 2 years after ketoconazole treatment.[15] No relapse of *Scedosporium* spp infection was reported in all cases. Follow-up was not mentioned in 14 reports. A follow-up period less than 12 months was reported in 11 cases. One case reported that the patient was lost to follow-up after discharge.[7] The follow-up duration varied from 6 weeks to 5 years (median 11 months).

The overall case mortality was 12.5% (5/40). The fatality rate was 9.09% (2/22) in cases with surgery,[32,33] while 16.67% (3/18) in cases without surgery (odds ratio, 0.50; 95% confidence interval, 0.07–3.38; $P=.48$).[25,38,39] There were 2 deaths reported after surgical therapy. One death happened on day 8 after surgical procedures due to respiratory failure.[33] The other death was not clearly reported.[32] Both of them had preoperative antifungal treatment, one with 2-hydroxy-stilbamidine[32] and the other one with voriconazole.[33] Three fatal cases were reported in patients without surgical treatment. One patient suddenly died on the 4th day of conventional antituberculous treatment after a positive sputum examination for acid fast bacilli, with no antifungal agent being administrated.[38] Two patients died of respiratory failure after theoretically appropriate antifungal treatment.[25,39] However, their lung *Scedosporium* infection was complicated by acute cerebral infarction[39] and dapsone hypersensitivity syndrome,[25] respectively, which might have worsened the condition and contributed to the fatal outcome.

The logistic regression found surgery was not associated with reduced mortality (odds ratio, 1.19; 95% confidence interval, 0.09–15.64; $P=.89$), adjusting for age, gender, and antifungal chemotherapy. The area under the ROC curve was 0.88 (Fig. 2).

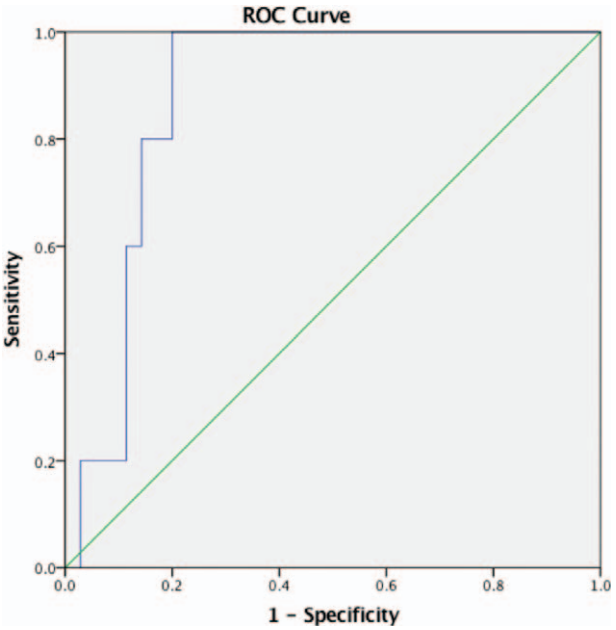

Figure 2. ROC curve for the predicted probabilities from BLR model. BLR = binary logistic regression, ROC = receiver operating characteristic.

4. Discussion

In this study, we found that surgical resection of affected lung tissues was performed in more than half of all immunocompetent patients with pulmonary *Scedosporium* infection, and it was not associated with better overall survival. Our model exhibited good performance in detecting such association, based on ROC curve analysis.

The following demographic, biological and methodological reasons may explain the relatively poor effect of surgery in our review. Firstly, cases in our study had no obvious evidence of immune defect. The therapeutic outcome of pulmonary *Scedosporium* infection may be largely associated with the immune status. Our study found that *Scedosporium* lung infection caused localized lesions and resulted in an overall mortality of 12.5% in immunocompetent patients. Chemotherapy alone could contribute to a favorable prognosis in this group of patients. However, *Scedosporium* spp could cause invasive and disseminated infections in immunosuppressed individuals, especially in solid organ transplant recipients, and lead to mortality as high as 50% to 100%.[5,40–44] Therefore, the morality was much lower in paints with normal immune defense. For immunocompromised patients, as failure of antifungal treatment is much more common, surgical resections may be helpful in improving the survival.[45]

Secondly, *S apiospermum* and *P boydii* were isolated from the majority cases included in our study. As the nomenclature of this group of fungi has changed several times in the course of history due to taxonomic developments, the formerly used names were reported in old literature. *Monosporium apiospermum* (*M apiospermum*) as the old name for *S apiospermum* was reported in 4 cases that published before 1969. *Allescheria boydii* (*A boydii*) and *Petriellidium boydii* as the formerly used names for *Pseudallescheria boydii* (*P boydii*) were reported in 3 and 4 cases, respectively, mainly before 1982. Although in vitro and in vivo data revealed that *S apiospermum* and *P boydii* were resistant to amphotericin B and flucytosine, they demonstrated variable

susceptibility to itraconazole, voriconazole, posaconazole, and micafungin. By comparison, *S prolificans* often exhibits typical high-level intrinsic resistance to all currently available antifungal agents and surgery may be the only effective therapeutic options for this pathogen.[4,6] Two cases reported a positive culture of *S prolificans* in our review, and both of them were successfully treated with surgery.[20,30] Due to the scarcity of cases with *S prolificans*, we failed to conduct a subgroup analysis to address the effect of surgery in different *Scedosporium* species.

Thirdly, a longer-term prognosis could not be evaluated to appreciate the longer-term effect of surgical therapy in our review. Assessment of clinical outcome and treatment efficacy depends on reliable follow-up duration. In the studies investigating surgical effect on long-term survival in patients with pulmonary aspergillosis or lung cancers, a 5-year follow-up was always conducted.[46,47] The median follow-up duration was 11 months in our review. Therefore, the current result might just show a relatively short-term effect of surgery on patient survival. Besides, we did not observe any relapse from cases in our review. A comparatively longer-term follow-up may be more reliable to identify late relapse. Nevertheless, it is worth to notice that a 5-year follow-up was conducted in 2 cases in our study.[27,29] One case reported a 73-year-old woman who developed *S apiospermum* lung infection and a pulmonary tumorlet.[29] The other case reported a 40-year-old woman who had right lower cystic bronchiectasis and *S apiospermum* colonization.[27] Lobectomy was performed without any antifungal treatment in both cases, and no recurrence occurred during the 5-year follow-up period.

Although there was a recommendation of triple therapy (a combination of azole, echinocandin, and polyene) as 1st-line treatment against *Scedosporium* spp infections, our data could not show the superiority of multiple-drug therapy compared with monotherapy because of the limited cases. From a clinical perspective, the resistance status of these fungi and the severity of infection may advocate a broad antifungal combination therapy. Strong synergistic activity with decreased toxicity has been proved for combination use of antifungal agents. Previous study showed that for pulmonary fungal infections due to *Scedosporium*/*Lomentospora*, triple and double therapy was superior to monotherapy regarding FEV1, radiology, and symptoms in patients with cystic fibrosis.[48] However, a better effect of combined therapy in patient survival has not been proven yet. Variable outcomes of combination therapy in clinical scenarios further highlight the necessity for more studies in this area.[49,50] As host factors may affect the efficacy of antifungal agents in the clinical setting, we consider that patients with unimpaired immune condition may have a better response to chemotherapy.

The median time to diagnosis of *Scedosporium* infection was 5.5 months in our review, much longer than the time reported in cases after near-drowning.[51] Delays in diagnosis may lead to inappropriate treatment with grave consequences, especially in immunocompromised patients. A fast and correct etiological diagnosis could improve the patient's outcome in any case. For *Scedosporium* infections, the lack of specific symptoms and imaging findings may lead to empirical antibiotics or antituberculosis therapy before antimycotics administration. Identification of *Scedosporium* spp currently depends upon histological detection of hyphal structures in clinical specimens and the molecular confirmation of their presence. However, a timely diagnosis is sometimes difficult in clinical practice. First of all, the low sensitivity of routine culture methods would prevent positive detection of filamentous fungi. In the current review, we found that negative results of BAL fluid and sputum examinations were usually repeated before a final positive confirmation. Comparatively, biopsy samples seemed to be more reliable for the detection of *Scedosporium* spp. However, lung biopsy through invasive procedures of bronchoscopy and thoracoscopy may put the patients at a high risk of bleeding and pneumothorax. Moreover, it may be difficult to distinguish *Scedosporium* spp from species of *Fusarium* or *Aspergillus* in practice, as all of them present dichotomous branching, hyaline hyphae, and regular hyphal septation.[24,52] Given these difficulties, newer approaches have been pursued for clinical microbiological diagnosis of *Scedosporium* spp, including nonculture-based molecular methods that utilize nucleic acid sequencing and mass spectroscopy.[53]

After positive detection of fungi in specimens from patients, clinicians have to determine whether this is harmless contamination or colonization or active infection requiring specific treatment. It is not always easy to ascertain, as this group of pathogens is ubiquitous in the environment. However, *Scedosporium* spp are isolated in 1% of dwellings and do not appear to be frequent colonizers of humans.[54] We considered all cases in our study have active *Scedosporium* infection rather than colonization or contamination because: opportunistic fungus colonization is less likely to happen in immunocompetent cases, especially in those without underlying lung diseases; all cases had several episodes of clinical symptoms leading to admission or treatment; and all cases showed dynamic changes in CT imaging or clinical symptoms before and after antifungal therapy.

This study has a potential limitation that should be noted. Pre- and/or postoperative chemotherapy was used in 11 patients in our review. Although the disease severity could not be evaluated in cases, there is a fact that a combined surgical and antifungal therapy would be more frequently conducted in more severe cases, which may impact the case fatality rate. Therefore, making a subgroup analysis according to surgery with or without antifungal therapy may be more reliable for the evaluation of surgical efficacy. However, we were unable to assess the impact due to the small number of patients included in our study, so a potential bias could not be ignored in the result.

Case reports and case series with good methodological quality help to advance our knowledge by describing new or notable events transparently and in detail. Risk of bias in included reports might limit the review in producing a comprehensive summary of the effect of surgery. In our study, 2 case series did not explicitly describe the representativeness of reported cases or a selection method, leaving the readers with uncertainty to whether it was the whole experience of the researchers and indicating possible selection bias.[28,55] Included cases reported a median follow-up of 11 months. Based on the currently available data, the long-term effect of surgery on mortality and later relapse was unable to be assessed. Therefore, causality bias could not be ignored in cases with no follow-up or a short-term follow-up. Sufficient details in case reports/series allow readers to apply the evidence derived from the report in their own practice. Lack of enough information on treatment duration in some cases resulted in the risk of reporting bias. The CAse REport (CARE) guidelines should be followed to reduce bias, increase the accuracy, transparency, and usefulness of case reports/series.[56]

5. Conclusions

In conclusion, surgical therapy may not be associated with reduced mortality in immunocompetent patients with pulmonary

Scedosporium spp infection. Surgical excision could be considered but is not imperative for this group of patient. More reports of similar cases with longer-term follow-up are essential for a better understanding of the long-term effect of surgery in the treatment of this rare pathogen.

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