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BRIEF REPORT

Determinant of 30-Day Mortality of Pulmonary Legionellosis: Do Coinfections Matter?

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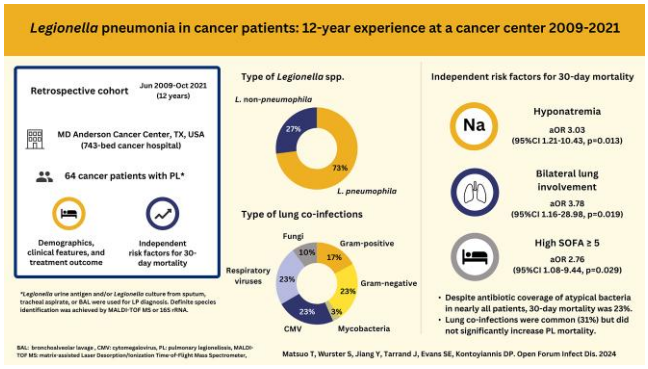
We retrospectively reviewed 64 cases of cancer with pulmonary legionellosis (*Legionella pneumophila* in 73%). Nearly all patients received *Legionella*-active antibiotics, yet 30-day mortality was 23%. Independent predictors of 30-day mortality were hyponatremia, bilateral lung involvement, and Sequential Organ Failure Assessment score ≥5. Lung coinfections were common (31%) but did not significantly increase mortality.

Graphical Abstract



Keywords. cancer; coinfections; *Legionella*; mortality outcomes; pneumonia.

Pulmonary legionellosis (PL) is a global opportunistic infection caused by the inhalation of aerosolized water particles laden with *Legionella* spp. Patients who are immunocompromised, especially those with hematologic malignancies or recipients of hematopoietic stem cell transplantation or solid organ transplantation, are at a heightened risk for developing PL [1–6], with mortality rates ranging from 27% to 65% [1–4].

Recent advances in diagnostic technologies, such as matrix-assisted laser desorption ionization–time of flight mass spectrometry and 16S ribosomal RNA sequencing, have resulted in an increasing number of reports that identify *Legionella* species other than *Legionella pneumophila* serogroup 1 as the causative agent of PL, especially among patients who are immunosuppressed [2, 4, 6]. Additionally, there has been a growing body of literature reporting various viral, bacterial, and fungal coinfections in patients with PL [4, 6, 7]. Therefore, we reviewed the epidemiology, risk factors, clinical characteristics, and outcomes of PL, including the impact of coinfections, in a contemporary cohort of patients with cancer and PL at a tertiary cancer center.

METHODS

We retrospectively reviewed the records of all adult patients with cancer (≥18 years old) who were diagnosed with PL at The University of Texas MD Anderson Cancer Center from January 2009 to October 2021. PL diagnosis was confirmed through either a *Legionella* urine antigen test (UAT; BinaxNOW [Alere Inc]) or culture from sputum, tracheal aspirates, or bronchoalveolar lavage samples with selective and nonselective buffered charcoal yeast extract agar plates. Species identification was performed with either matrix-assisted laser desorption ionization–time of flight mass spectrometry (Vitek MS; BioMérieux) or 16S ribosomal RNA gene sequencing [8]. Collected data, definitions of variables, diagnostic criteria/workup for lung coinfections, and statistical methods are provided in the supplementary methods and Supplementary Table 1.

RESULTS

We identified 64 cases of cancer with PL: 45 patients (70%) were male and the median age was 60 years. Most patients (n = 42, 66%) had hematologic malignancies. A history of hematopoietic stem cell transplantation was present in 20 patients (31%). Lymphopenia was common at PL diagnosis (n = 48, 75%), whereas neutropenia was noted in only 16 patients (25%; Table 1).

Cough (84%), fever (81%), dyspnea (69%), and hypoxia (66%) were common. Headache (13%), diarrhea (13%), nausea/vomiting (9%), and confusion (9%) were less frequent. Hyponatremia and

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Table 1. Patients With and Without 30-Day Mortality

Characteristic	Survived (n = 49)	Died (n = 15)	Total (n = 64)	*P* Value
Male sex	35 (71)	10 (67)	45 (70)	.753
Age, y	64 (53–69)	58 (45–61)	60 (52–68)	.068
Race and ethnicity				>.999
Non-Hispanic White	35 (71)	11 (73)	46 (72)	
Hispanic	9 (18)	3 (20)	12 (19)	
African American	2 (4)	1 (7)	3 (5)	
Asian	3 (6)	0 (0)	3 (5)	
Body mass index	27 (25–31)	26 (20–33)	27 (24–31)	.379
Smoking				>.999
None	27 (55)	8 (53)	35 (55)	
Current	5 (10)	1 (7)	6 (9)	
Former	17 (35)	6 (40)	23 (36)	
Alcohol				**.043**
None	30 (61)	14 (93)	44 (69)	
Current	18 (37)	1 (7)	19 (30)	
Former	1 (2)	0 (0)	1 (2)	
Malignancy type				.473
Hematologic	31 (63)	11 (73)	42 (66)	
Solid	18 (37)	4 (27)	22 (34)	
Active malignancy status at diagnosis of PL	45 (92)	13 (87)	58 (91)	.618
Active chemotherapy[a]	31 (63)	12 (80)	43 (67)	.348
Corticosteroid use	10 (20)	5 (33)	15 (23)	.315
History of HSCT	14 (29)	6 (40)	20 (31)	.526
Type of HSCT				.778
Allogenic	9/14 (64)	4/6 (67)	13/20 (65)	
Autologous	5/14 (36)	2/6 (33)	7/20 (35)	
Graft-vs-host disease	5/9 (56)	2/4 (50)	7/13 (54)	>.999
Other underlying risk factors				
Diabetes	9 (18)	1 (7)	10 (16)	.429
Chronic lung disease	6 (12)	1 (7)	7 (11)	>.999
Chronic kidney disease	3 (6)	0 (0)	3 (5)	>.999
Chronic heart failure	2 (4)	0 (0)	2 (3)	>.999
History of splenectomy	1 (2)	0 (0)	1 (2)	>.999
Neutropenia at diagnosis, neutrophils/μL	10 (20)	6 (40)	16 (25)	.173
500–1000	2 (4)	2 (13)	4 (6)	
100–500	5 (10)	3 (20)	8 (13)	
<100	3 (6)	1 (7)	4 (6)	
Lymphopenia at diagnosis, lymphocytes/μL	38 (78)	10 (67)	48 (75)	.498
500–1000	4 (8)	0 (0)	4 (6)	
100–500	28 (57)	8 (53)	36 (56)	
<100	6 (12)	2 (13)	8 (13)	
Clinical presentation of PL				
Cough	42 (86)	12 (80)	54 (84)	.687
Fever	40 (82)	12 (80)	52 (81)	>.999
Dyspnea	32 (65)	12 (80)	44 (69)	.354
Hypoxia	31 (63)	11 (73)	42 (66)	.473
Headache	8 (16)	0 (0)	8 (13)	.181
Diarrhea	8 (16)	0 (0)	8 (13)	.181
Nausea/vomiting	6 (12)	0 (0)	6 (9)	.322
Confusion	5 (10)	1 (7)	6 (9)	>.999
Pleuritic chest pain	5 (10)	0 (0)	5 (8)	.329
Clinical laboratory findings				
Elevated liver enzyme	27 (55)	10 (67)	37 (58)	.427
Hyponatremia	15 (31)	10 (67)	25 (39)	**.012**
Acute kidney injury	11 (22)	6 (40)	17 (27)	.197

Table 1. Continued

Characteristic	Survived (n = 49)	Died (n = 15)	Total (n = 64)	*P* Value
Computed tomography findings[b]	47	12	59	
Airspace consolidation	42 (89)	11 (92)	53 (90)	>.999
Ground glass opacities	34 (72)	10 (83)	44 (75)	.712
Multilobar infiltrate	32 (68)	10 (83)	42 (71)	.478
Adenopathy	30 (64)	8 (67)	38 (64)	>.999
Nodules	30 (64)	6 (50)	36 (61)	.510
Pleural effusions	26 (55)	8 (67)	34 (58)	.478
Mass-like consolidation	13 (28)	4 (33)	17 (29)	.729
Halo sign	5 (11)	0 (0)	5 (9)	.573
Cavitation	3 (6)	0 (0)	3 (5)	>.999
Reversed halo sign	2 (4)	0 (0)	2 (3)	>.999
Bilateral	27 (57)	11 (92)	38 (64)	**.041**
Legionella type				.740
L pneumophila	35 (71)	12 (80)	47 (73)	
Legionella, not *pneumophila*	14 (29)	3 (20)	17 (27)	
Coinfections[c]	16 (33)	4 (27)	20 (31)	.759
Bacterial	7 (14)	2 (13)	9 (14)	>.999
Viral	9 (18)	2 (13)	11 (17)	>.999
Fungal	1 (2)	2 (13)	3 (5)	.134
SOFA at PL diagnosis	3 (2–5)	6 (4–7)	4 (2–6)	.051
Time to PL diagnosis from admission, median (range)	0 (1–13)	2 (0–10)	2.5 (0–13)	.055
Infectious diseases consultation	46 (94)	13 (87)	59 (92)	.583
Treatment for PL[d]				.487
Monotherapy	35 (71)	12/14 (86)	47/63 (75)	
Combination	14 (29)	2/14 (14)	16/63 (25)	
Levofloxacin-containing regimen	30 (61)	10 (67)	40 (63)	.546
Time to initiation of appropriate antibiotics[d] from admission, d	0 (0–1)	0 (0–1)	0 (0–1)	.268
Intensive care unit stay within 1 wk of PL diagnosis	6 (12)	11 (73)	17 (27)	**<.0001**

Data are presented as No. (%) and median (IQR) unless noted otherwise. Bold *P* values indicate $P < .05$.

Abbreviations: HSCT, hematopoietic stem cell transplantation; PL, pulmonary legionellosis; SOFA, Sequential Organ Failure Assessment.

[a]Active chemotherapies were administered within 90 days of PL diagnosis.

[b]Computed tomography findings were obtained within 7 days before or after PL diagnosis.

[c]Three patients had >1 category of copathogens (2 with bacteria and virus, 1 with virus and fungus).

[d]Antibiotics having activity against *Legionella*, including levofloxacin, azithromycin, and doxycycline.

acute kidney injury were observed in 39% and 27% of cases, respectively. Elevated liver enzymes were common (58%). The commonest computed tomography findings were airspace consolidation (90%), ground glass opacities (75%), and multilobar infiltrates (71%). Bilateral lung involvement was also frequent (64%).

Forty-seven PL cases (73%) were caused by *L pneumophila* (Figure 1*A*). The commonest non-*pneumophila* species isolated were *L longbeachae* (6%) and *L anisa* (5%). Notably, the proportion of non-*pneumophila* species was 34%. The median time to diagnosis of PL was 2.5 days overall (range, 0–13); it was shorter for *L pneumophila* than for non-*pneumophila* species (median, 2 vs 13 days; $P < .01$).

Twenty patients (31%) had coinfections: bacterial (14%, mainly gram-negative rods), viral (17%, mainly respiratory viruses and cytomegalovirus), and fungal (5%; Figure 1*B*). Of those, 5 patients (25%) had >1 copathogen. We compared the clinical characteristics and outcomes of patients with and without lung coinfections (Supplementary Table 2). No significant differences between the cohorts were found, except for younger age (median, 56 vs 64 years; $P = .034$), a higher proportion of Hispanic patients (40% vs 9%, $P = .016$), and patients with a history of hematopoietic stem cell transplantation (55% vs 20%, $P = .009$) in the coinfection group. Of note, the presence of coinfections did not significantly affect 30-day mortality ($P = .759$).

We further compared the clinical characteristics and outcomes of patients with hematologic malignancies and solid tumors (Supplementary Table 3). A higher Sequential Organ Failure Assessment (SOFA) score was found in the hematologic malignancy group as compared with the solid tumor group (median, 5 vs 3; $P = .001$).

All but 1 patient received appropriate empiric antibiotics with activity against *Legionella* species after admission (median, 0 days; range, 0–7). Forty-seven patients (73%) were treated with monotherapy, including fluoroquinolones (n = 33), azithromycin (n = 9), or tetracyclines (n = 5). The remaining 16 patients (25%) received antimicrobial combination therapy, consisting of fluoroquinolone and azithromycin (n = 7),

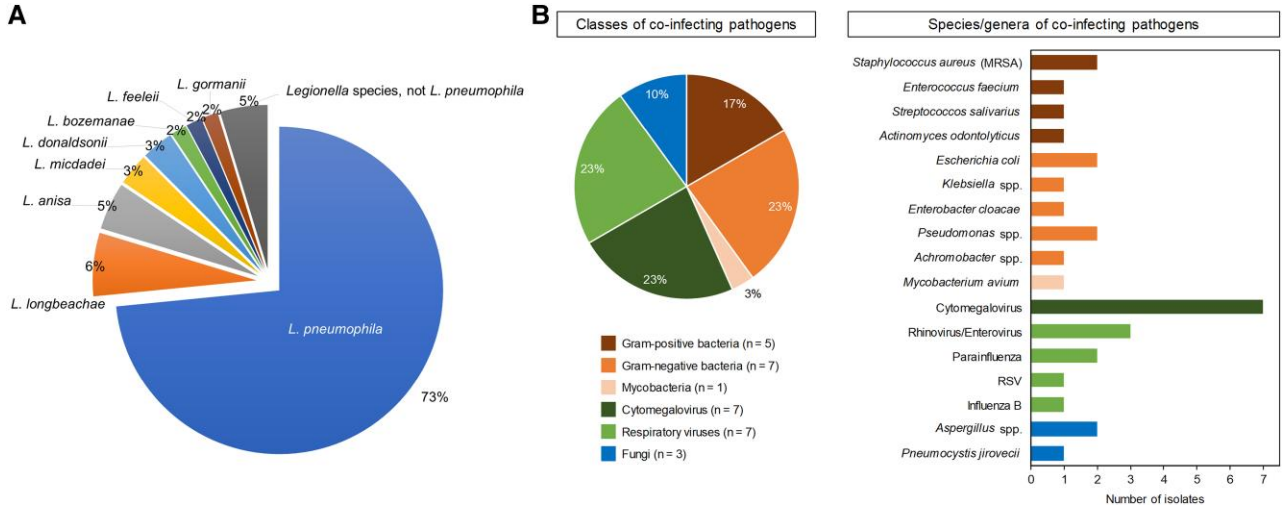

Figure 1. *A,* Types of *Legionella* spp. *B,* Types of coinfections (20 patients with 30 copathogens isolated). MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus.

fluoroquinolone and tetracycline (n = 7), or azithromycin and tetracycline (n = 2).

Fifteen patients (23%) died within 30 days after PL diagnosis. In univariate analysis, hyponatremia ($P = .012$), bilateral lung involvement ($P = .041$), and intensive care unit admission within 1 week of PL diagnosis ($P < .0001$) were significantly associated with 30-day mortality (Table 1). In contrast, malignancy type ($P = .473$), *Legionella* species ($P = .740$), neutropenia ($P = .173$) or lymphopenia ($P = .498$) at PL diagnosis, coinfections ($P = .759$), levofloxacin-containing regimen ($P = .546$), and combination therapy ($P = .487$) did not significantly affect 30-day mortality. Multivariable analysis identified the following as independent risk factors for 30-day mortality: hyponatremia (adjusted odds ratio [aOR], 3.03; 95% CI, 1.21–10.43; $P = .013$), bilateral lung involvement (aOR, 3.78; 95% CI, 1.16–28.98; $P = .019$), and SOFA score ≥5 at PL diagnosis (aOR, 2.76; 95% CI, 1.08–9.44; $P = .029$; Supplementary Table 4).

Finally, we compared the clinical characteristics and outcomes of patients with *L pneumophila* and non-*pneumophila* species (Supplementary Table 5). Interestingly, a higher proportion of viral coinfection was found in the non-*pneumophila* group as compared with the *pneumophila* group (24% vs 4%, $P = .038$). Patients with non-*pneumophila* species were more likely to receive antibiotic combination therapy than those with *L pneumophila* (47% vs 17%, $P = .010$). Thirty-day mortality was comparable between patients with non-*pneumophila* species and those with *L pneumophila* (18% vs 26%, $P = .740$), although the time to appropriate empiric treatment after admission for the non-*pneumophila* group (median, 1 day; IQR, 0–4) was longer than for the *pneumophila* group (median, 0 days; IQR, 0–1; $P = .007$).

DISCUSSION

To our knowledge, this study represents one of the largest contemporary cohorts of patients with cancer and PL. Despite appropriate empiric antimicrobial treatment, the high mortality rate of 23% aligns with previous studies and underscores the persistence of poor outcomes of PL in this vulnerable population [1, 2]. Thirty-nine percent of our patients had hyponatremia; however, it is unclear if this is a differentiating feature of PL in our population, because hyponatremia is commonly observed in patients with various malignancies [9]. Moreover, it is commonly associated with PL in patients with community-acquired pneumonia [10]. Although a combination of inappropriate antidiuretic hormone secretion, interstitial nephritis, and Fanconi syndrome has been described as a cause of hyponatremia in patients with PL [11, 12], the detailed pathophysiologic mechanisms have never been conclusively identified [13, 14].

We also identified hyponatremia, bilateral lung involvement, and a SOFA score >5 as poor prognostic factors. Given that hyponatremia has been associated with the severity of PL [15], it may be a marker for increased mortality. However, hyponatremia as prognostic factor in PL is questionable, as low serum sodium is a well-recognized poor prognostic factor in patients with malignancies [9]. The increased mortality of patients with bilateral lung involvement aligns with previous research on community-acquired pneumonia [16].

Notably, our study identified a high prevalence of lung coinfections in patients with cancer and PL (31%). This observation has implications for clinical management of PL, as coinfections such as gram-negative bacteria, respiratory viruses, and cytomegalovirus add complexity to the diagnosis and assessment of treatment response in PL. Although the frequent coinfections could reflect the severe net state of immunosuppression

in our patients, *Legionella* is known to have pleiotropic effects on pulmonary and systemic host immune defense [17], including epithelial damage, changes in airway function, airway leakage, and delayed tissue repair, as well as altered cellular recognition, inflammatory responses, and immune cell recruitment to the airways [18, 19]. Whether these pathophysiologic changes could predispose patients to excess coinfections remains unclear.

As is the case in patients without cancer and consistent with previous reports [2, 4, 6], *L pneumophila* serogroup 1 was the predominant *Legionella* species in our cohort of patients with cancer and can be readily identified with UATs. In contrast, the majority of UATs cannot detect serogroups of *L pneumophila* other than serogroup 1 and non-*pneumophila* species [20]. We found that 25% of patients with PL had non-*pneumophila* species, underscoring a need for clinicians to consider further workup with culture or molecular techniques if PL is a consideration [20]. This is especially important in high-risk cases with hematologic malignancies, as previous research suggested a significantly higher proportion of non-*pneumophila* PL in patients with hematologic malignancies [6]. Consistent with our previous institutional cohort [2], the mortality associated with non-*pneumophila* species was similar to that of the *L pneumophila* group. However, the time to appropriate treatment was longer for the non-*pneumophila* group than for *L pneumophila*, likely due to delayed diagnosis.

Furthermore, the observation that the majority of patients (59%) had a low SOFA score challenges the classical view of PL as a severe form of community-acquired pneumonia, suggesting that immunosuppression might modulate the inflammatory drivers of presentation, leading to milder clinical manifestations than traditionally expected, although the underlying mechanisms remain unclear.

Our study has several limitations. First, its single-center nature may affect the generalizability of our findings. Second, not all patients underwent bronchoalveolar lavage, which could have affected the detection of copathogens. Third, this study arises from the potential selection bias present in our data set, which was skewed toward more severe cases of PL, due to the exclusion of outpatients who were empirically treated with quinolones or macrolides without a diagnostic workup. Fourth, we acknowledge that true copathogens and colonizers cannot always be distinguished reliably in a retrospective study. Although some pathogens, such as *Actinomyces*, viridans group streptococci, and *Enterococcus*, might be bystanders instead of true copathogens, we included these as copathogens based on reports that they were causative pathogens in patients with cancer [21–23]. Last, given the diagnostic gap of UAT, PL due to non-*pneumophila* species has likely been underdiagnosed and thus underrepresented in this study, as bronchoalveolar lavage or sputum studies were not routinely performed.

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

Author contributions. D. P. K. was responsible for study concept and design. T. M. and J. T. were responsible for acquisition of the data. T. M. wrote the first draft of the manuscript. Y. J. contributed to the data analysis. S. W. and S. E. E. provided critical comments. All authors were responsible for interpretation of the results and revision of the manuscript.

Previous presentation. Parts of our results were presented during a poster presentation at IDWeek, 19–23 October 2023, Washington, DC.

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Potential conflicts of interest. D. P. K. reports honoraria and research support from Gilead Sciences and Astellas Pharma. He also received consultant fees from Astellas Pharma, Merck, and Gilead Sciences and is a member of the Data Review Committee for Cidara Therapeutics, AbbVie, Scynexis, and the Mycoses Study Group. All other authors report no potential conflicts.

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