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ORIGINAL ARTICLE

Community-acquired versus nosocomial *Legionella* pneumonia: factors associated with *Legionella*-related mortality

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Abstract

Over the past decade, changes in the diagnosis and management of *Legionella* pneumonia occurred and risk factors for severe infection and increased mortality were identified. Previous reports found that nosocomial infection is associated with higher mortality while others showed no differences. We aimed to evaluate the differences in the clinical course and mortality rates between hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP) caused by *Legionella pneumophila*. A retrospective cohort study of patients admitted due to *Legionella* pneumonia between January 2012 through November 2019 was conducted in a tertiary referral center (Rambam Health Care Campus, Haifa, Israel). The primary outcome was 30-day *Legionella* pneumonia–related mortality. A multivariable logistic regression was performed to determine whether a nosocomial infection is an independent predictor of mortality. One hundred nine patients were included. Seventy (64.2%) had CAP and 39 (35.8%) had HAP. The groups were comparable regarding age, gender, and comorbidities. Time to diagnosis was longer and the number of patients receiving initial empiric anti-*Legionella* spp. treatment was smaller in the HAP group (8 days [IQR 5.5–12.5] vs. 5 days [IQR 3–8], $p < 0.001$ and 65.5% vs. 78.6%, $p = 0.003$, respectively). Patients with HAP had higher 30-day mortality, 41% vs. 18.6%, $p = 0.02$. In a multivariable logistic regression model, only pneumonia severity index and nosocomial source were independently associated with increased mortality. HAP caused by *Legionella* spp. is independently associated with increased mortality when compared to CAP caused by the same pathogen. The possible reasons for this increased mortality include late diagnosis and delayed initiation of appropriate treatment.

Keywords *Legionella* pneumonia · Community-acquired pneumonia · Healthcare-associated pneumonia · Nosocomial infections

Introduction

Legionella pneumophila is an important cause of community-acquired and nosocomial pneumonia [1]. The reported incidence of *Legionella* pneumonia ranges from approximately 1.4 cases per 100,000 persons in the United States and Europe to 1.8 and 5.4 cases in Australia and New Zealand, respectively [2–5]. *Legionella* pneumonia accounts for about 2 to 15% of all cases of community-acquired pneumonia (CAP) that require hospitalization in Europe and North

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America [6]. The incidence of the disease is rising, and it is especially common among those who require admission to intensive care units [3, 7]. In many series, infection with *Legionella* spp. ranks among the three most common causes of severe CAP and is isolated in 1–40% of cases of severe HAP [8, 9]. According to some reports, approximately 20% of the cases of Legionnaires' disease were acquired in healthcare facilities [10].

Up-to-date guidelines suggest microbiologic evaluation and empiric antibiotic coverage for *Legionella* spp. for all severe cases of CAP. However, these measures are not recommended for patients with HAP [11]. Among patients hospitalized with *Legionella* spp. infection, high mortality rates were found in the elderly and those with comorbidities, as well as among smokers and patients who had a delay in diagnosis and appropriate treatment [1]. Some reports from the 1990s found that nosocomial origin of infection is independently associated with higher case fatality rates while in other series no such difference was observed [12–16]. Reports from recent years are lacking.

The objective of this study was to evaluate whether hospital-acquired *Legionella* pneumonia is associated with increased mortality and a different clinical course compared to community-acquired *Legionella* pneumonia.

Material and methods

Study design, measures, and variables

We conducted a population-based retrospective cohort study, using the data of patients who were hospitalized in Rambam Health Care Campus (RHCC) and found positive for *Legionella* spp. infection either by polymerase chain reaction (PCR), urinary antigen test (Binax Legionella urinary antigen by Alere, Scarborough, USA), or culture on buffered charcoal yeast extract (BCYE) Agar (Hy-Laboratories, Israel) [17], between January 1, 2012 and November 30, 2019. The patients were identified from a review of infection control and microbiology laboratory records. Only patients with clinical symptoms and signs of pneumonia were included in the study.

RHCC is a 1000-bed tertiary, academic hospital serving over 2 million residents in northern Israel with 80,000–90,000 inpatient admissions every year.

The study was approved by the Institutional Review Board at Rambam Health Care Campus (approval number RMB-0593-19). The need for written informed consent was waived due to the retrospective study design.

Data analyzed in this study were retrieved from Prometheus, RHCC integrated electronic medical records system. Using a structured form, two abstractors, trained to use the data collection instrument, reviewed all the charts independently. Chart review was conducted following published guidelines for the performance of retrospective studies [18]. Disagreement between the investigators was resolved by discussion. The computed tomography (CT) scans and chest X-rays were reviewed separately by a radiologist who was blinded to all other patient data. In concordance with the Centers for Disease Control and Prevention (CDC) definition, HAP was defined as pneumonia that presented more than 48 h after hospital admission, without any clinical evidence that the pathogen was already in the incubation phase before admission [19].

The following data were retrieved from the electronic medical records of the patients:

1. Demographics: age, gender, home, or long-term care facility residency.
2. Vital signs and laboratory values at admission or when new-onset respiratory symptoms/fever appeared in an already hospitalized patient.
3. Pneumonia severity index (PSI) at admission or when new-onset respiratory symptoms/fever appeared in an already hospitalized patient was calculated. This score incorporates age, gender, nursing home residency, neoplastic disease, liver disease history, congestive heart failure, cerebrovascular disease, renal disease, vital signs, pH, BUN, sodium, glucose, hematocrit, and presence of pleural effusion on chest radiography [20].
4. Comorbidities: smoking history (in concordance with the CDC definition, former smoker was defined as a patient who has smoked at least 100 cigarettes in his/her lifetime but who had quit smoking at the time of interview)[21], chronic obstructive lung disease, ischemic heart disease, Charlson comorbidity index, hypertension, diabetes mellitus, cerebrovascular disease, congestive heart failure, immunosuppressive therapy, and active solid or hematologic malignancy.
5. Clinical course: time to diagnosis (for nosocomial infection this time was defined as the time from new-onset respiratory symptoms and/or fever to the diagnosis of *Legionella* infection); initial antibiotic treatment; adequate anti-*Legionella* treatment (defined when containing either macrolides, levofloxacin, or tetracyclines); duration of anti-*Legionella* antibiotic treatment; time to clinical stability (defined as time to all of the following: fever < 37.2, heart rate < 100 beats per minute, respiratory rate < 24 breaths per minute, oxygen saturation while breathing ambient air above 92% [not applicable to patients on chronic oxygen therapy]); need for dialysis; intensive care unit (ICU) admission; need for mechanical ventilation; acute kidney injury (defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h, or ≥ 1.5 times baseline) [22]; and 30-day *Legionella*-related mortality (defined as death directly attributed to respiratory complications of the acute disease).

6. Radiologic findings: chest radiographs and computed tomography scans (CT) were interpreted by a radiology fellow. We selected the first chest X-ray or CT performed during the first 3 days of care (after admission or after new-onset respiratory symptoms in hospitalized patients). We determined the presence of pleural effusion and parenchymal opacities.

Statistical analysis

Patients' characteristics were summarized with descriptive statistics. Mean (standard deviation, SD) and median (interquartile range, IQR) were used for the description of normally and non-normally distributed quantitative variables, respectively. Distribution normality was determined using histograms. Normally distributed values were compared using independent sample Student's *t* test while the Mann-Whitney test was utilized for non-normally distributed covariates. The Chi-squared test was used to analyze the differences between categorical variables. Multivariate forward stepwise logistic regression was performed to assess the relationship between the characteristics and 30-day mortality. Variables were selected as candidates for the multivariate analysis on the basis of the level of significance of the bivariate association ($p < 0.1$). $p < 0.05$ was considered to be statistically significant. Missing data were handled using list-wise deletion. Data analysis was conducted with Statistical Package for the Social Sciences, version 23.0 (SPSS, Chicago, IL, USA) and Microsoft Excel version 14.0 (Microsoft Corporation, Redmond, Washington).

Results

During the study period, 8548 hospitalized patients were tested for *Legionella* spp. in RHCC either by PCR, urinary antigen test, or culture. Of these, 111 (1.3%) patients had positive results. Eighty-one (74.3%) patients had positive urine antigen, 35 (32.1%) had positive sputum PCR, and 8 (3.3%) had a positive culture. In 13 (11.9%) patients, the diagnosis was confirmed by 2 or more methods. Two patients had a non-pulmonary *Legionella* infection (endocarditis and cervical abscess) and were excluded. One hundred patients were included in the final analysis, 70 (64.2%) of whom had a community-acquired infection and 39 (35.8%) had a nosocomial disease. The baseline demographic and clinical characteristics of the patients included in the study are presented in Table 1.

Patients with HAP were comparable to patients with CAP regarding age, gender, and comorbidities. Fewer patients with hospital-acquired infection had chronic renal failure (28.6% vs. 10.3%, $p = 0.048$). However, these patients had more hematologic malignancies (51.3% vs. 22.9%, $p = 0.005$) and more of them were immunocompromised (71.8% vs. 47.1%, $p = 0.02$). The etiology of immunosuppression among 61 immunocompromised patients is presented in Table 2.

The initial clinical manifestation of *Legionella* infection was comparable, although patients with HAP had less confusion at diagnosis (15.4% vs. 38.6%, $p = 0.001$) and less hyponatremia (38.5% vs. 80%, $p < 0.001$). Leukopenia and anemia were more prevalent in the HAP group (33.3% vs. 14.29%, $p = 0.03$ and 94.9% vs. 62.9%, $p < 0.001$, respectively). Both groups were comparable regarding baseline vital signs and PSI.

The median time to diagnosis in the entire cohort was 6 days (IQR 4-9). It was significantly longer in patients with hospital-acquired infection (8 days [IQR 5.5–12.5] vs. 5 days, [IQR 3–8], $p < 0.001$). More patients in the CAP group were diagnosed by urine antigen test (85.7% vs. 53.9%, $p < 0.001$) and initially (before a definitive diagnosis of *Legionella* infection) treated by anti-*Legionella* agent (78.6% vs. 65.5%, $p = 0.003$). Patients with HAP had a more complicated clinical course as demonstrated by a longer time until clinical stability (4 days [IQR 2–7] vs. 9 [IQR 4–18], $p = 0.02$) and prolonged length of stay (25 days [IQR 13.5–37.5] vs. 7 days [IQR 5–12], $p < 0.001$). Patients with hospital-acquired infection had a twice higher chance of 30-day *Legionella*-related mortality, 41% vs. 18.6%, $p = 0.02$. Other details regarding the presenting symptoms and signs, as well as clinical course and outcomes, are presented in Table 3.

Among immunocompromised patients with community-acquired infection, 7 (21.2%) died due to *Legionella*-related complications compared to 9 (32%) with nosocomial infection ($p = 0.5$). In the subgroup of 61 immunocompromised patients, the association between hospital acquisition of *Legionella* and mortality rate did not reach statistical significance (OR 1.48, 95% CI 0.48–4.55, $p = 0.49$).

Chest X-rays were performed at symptoms onset/admission in 104 (95.4%) patients. Fifty (48.1%) patients had bilateral parenchymal opacities, and 50 (48.1%) had pleural effusion which was bilateral in 21 (20.19%) subjects. CT was performed in 46 (42.2%) patients. The radiological characteristics of the X-rays and CT scans are presented in Table 4. Patients with HAP had a significantly higher likelihood of having bilateral findings in chest radiography. These differences did not reach statistical significance on CT scans.

A univariable and multivariable regression model that included PSI, smoking status, recent antibiotic treatment, recent hospitalization, ischemic heart disease, diabetes mellitus, chronic obstructive lung disease, cerebrovascular disease, cognitive impairment, corticosteroid therapy, immunocompromised state, gastrointestinal complaints at admission, elevated liver enzymes at admission, thrombocytopenia, and white blood cell count identified only 2 risk factors associated with increased 30-day *Legionella*-related mortality: PSI (adjusted OR of 1.02 95% CI 1.01–1.03 for each one unit score increase, $p = 0.006$) and hospital-acquired infection (adjusted

Table 1 Baseline demographic and clinical characteristics of 109 patients included in the study

	Community-acquired *Legionella* pneumonia (n = 70)	Nosocomially acquired *Legionella* pneumonia (n = 39)	p value
Age, mean (± SD)	63.49 (± 12.99)	64.82 (± 16.95)	NS
Male gender, n (%)	47 (67.1%)	21 (53.9%)	NS
Nursing homes residents, n (%)	4 (5.8%)	6 (15.4%)	NS
Current or former smokers, n (%)	37 (52.9%)	17 (43.6%)	NS
Additional hospitalization (prior to the index admission) within the past 90 days, n (%)	21 (30%)	31 (79.5%)	**<0.001**
Antibiotic treatment within the past 90 days, n (%)	19 (31.7%)	18 (69.2%)	0.07
Ischemic heart disease, n (%)	21 (30%)	11 (28.2%)	NS
Diabetes mellitus, n (%)	25 (35.7%)	8 (20.5%)	NS
Chronic obstructive lung disease, n (%)	5 (7.1%)	5 (12.8%)	NS
Congestive heart failure, n (%)	7 (10%)	6 (15.4%)	NS
Chronic renal failure, n (%)	20 (28.6%)	4 (10.3%)	**0.048**
Cerebrovascular disease, n (%)	6 (8.6%)	1 (2.6%)	NS
Cognitive impairment, n (%)	3 (4.3%)	3 (7.7%)	NS
Hematologic malignancies, n (%)	16 (22.9%)	20 (51.3%)	**0.005**
Solid malignancies, n (%)	6 (8.6%)	8 (20.5%)	NS
Corticosteroid therapy, n (%)	15 (21.4%)	6 (15.4%)	NS
Immunosuppression, n (%)	33 (47.1%)	28 (71.8%)	**0.02**
Charlson comorbidity index, median (IQR)	6 (4–10)	8 (5–11)	0.1

SD standard deviation, *IQR* interquartile range, *NS* nonsignificant

OR of 3.45 95% CI 1.33–8.98, p = 0.01). Detailed results of the univariable and multivariable regression are presented in Table 1 in the supplementary material. The relationships between PSI, infection source (community vs. nosocomial), and 30-day mortality are demonstrated in Fig. 1.

Discussion

Our findings suggest that among hospitalized patients with *Legionella* pneumonia disease severity, defined by PSI, and hospital-acquired infection are independent, risk factors for 30-day mortality.

Previous reports have identified several risk factors for adverse outcomes among patients with *Legionella* infection, including age, immunosuppression, AIDS, malignancies in general and hematologic malignancies in particular, and chronic lung disease [14, 23–29]. Although nosocomial infection was found to be a risk factor in some studies, others found that the severity of hospital-acquired infection is equivocal to that acquired in the community settings when adjusted to other risk factors [14]. In our study, patients with hospital-acquired

Table 2 The etiology of immunosuppression among 61 immunocompromised patients included in the study

	Community-acquired *Legionella* pneumonia (n = 33)	Nosocomially acquired *Legionella* pneumonia (n = 28)
Prolonged (> 1 month) corticosteroids treatment, n (%)	15 (45.5%)	6 (21.4%)
Lymphohematologic malignancy, n (%)	15 (45.5%)	18 (64.3%)
Bone marrow transplants, n (%)	1 (3%)	5 (17.9%)
Chemotherapy for solid organ neoplasm, n (%)	5 (15.2%)	6 (21.4%)
Solid organ transplants, n (%)	3 (9.1%)	0 (0%)
Anti-tumor necrosis factor (TNF) treatment, n (%)	2 (6.1%)	2 (7.1%)
Anti-CD-20 treatment, n (%)	3 (9.1%)	0 (0%)

Some patients had more than one reason for immunosuppression

Table 3 Characteristics, clinical course, and outcomes of 109 patients included in the study cohort

	Community-acquired *Legionella* pneumonia (n = 70)	Nosocomially acquired *Legionella* pneumonia (n = 39)	p value
Presenting characteristics			
Confusion, n (%)	27 (38.6%)	6 (15.4%)	**0.001**
Oxygen saturation < 92%, n (%)	56 (80%)	33 (84.6%)	NS
Hypercapnia, n (%)	7 (14%)	9 (32.1%)	NS
Systolic blood pressure < 90 mmHg, n (%)	8 (11.4%)	6 (15.4%)	NS
Gastrointestinal complaints, n (%)	21 (30%)	8 (20.5%)	NS
Diagnosis by urine antigen test, n (%)	60 (85.7%)	21 (53.9%)	**< 0.001**
Elevated liver enzymes, n (%)	41 (62.1%)	17 (43.6%)	NS
Hyponatremia, n (%)	56 (80%)	15 (38.5%)	**< 0.001**
White blood cell > 11 K, n (%)	40 (57.1%)	19 (48.7%)	NS
White blood cell < 4.4 K, n (%)	10 (14.3%)	13 (33.3%)	**0.03**
Thrombocytopenia, n (%)	26 (37.1%)	22 (56.4%)	0.082
Anemia, n (%)	44 (62.9%)	37 (94.9%)	**< 0.001**
Pneumonia severity index, mean (± SD)	111.53 (± 40.23)	121.95 (± 34.3)	NS
Pneumonia severity index > 90, n (%)	45 (64.3%)	31 (79.5%)	NS
Clinical course			
Time to diagnosis (days), median (IQR)	5 (3–8)	8 (5.5–12.5)	**< 0.001**
Initial antibiotic treatment with anti-*Legionella* agent, n (%)	55 (78.6%)	19 (65.5%)	**0.003**
Treatment with macrolides, n (%)	26 (37.1%)	7 (18%)	0.06
Treatment with fluoroquinolones, n (%)	38 (54.3%)	27 (69.2%)	NS
Duration of anti-*Legionella* agent (days), median (IQR)	12.5 (7–14.5)	12.5 (6.5–21)	NS
Mechanical ventilation, n (%)	15 (21.4%)	12 (30.8%)	NS
Time to clinical stability (days), median (IQR)	4 (2–7)	9 (4–18)	**0.016**
Length of hospital stay (days), median (IQR)	7 (5–12)	25 (13.5–37.5)	**< 0.001**
Acute kidney Injury, n (%)	30 (42.9%)	16 (41%)	NS
ICU admission, n (%)	17 (24.3%)	17 (43.6%)	0.06
Dialysis, n (%)	7 (10%)	4 (10.3%)	NS
30-day *Legionella*-related mortality, n (%)	13 (18.6%)	16 (41%)	**0.021**

IQR interquartile range, *ICU* intensive care unit, *NS* nonsignificant

infection had a more complicated clinical course, with longer time to clinical stability, longer length of stay, and significantly higher infection-related mortality, independent of other risk factors. These differences in the clinical course may be explained by several factors. Patients with hospital-acquired infection were diagnosed later and fewer received empiric anti-*Legionella* coverage. These factors were previously shown to be associated with increased mortality [30, 31]. Current guidelines for the diagnosis and management of HAP do not recommend an empiric anti-*Legionella* coverage [11]. Although respiratory fluoroquinolones are occasionally used as empiric treatment of HAP, most patients are empirically treated with piperacillin-tazobactam, cefepime, or carbapenems. In addition, these guidelines recommend acquiring a microbiological specimen for culture but do not advise using the urinary antigen or *Legionella* PCR. This practice might be associated with a delayed diagnosis and appropriate antibiotic coverage in cases of *Legionella* infection. Indeed, in our cohort, only 53.85% of *Legionella* HAP was diagnosed by urine antigen testing as compared to 85.7% of the cases in the CAP group. Previous studies have shown a relationship between the increasing use of urine antigen testing, as a useful diagnostic tool for *Legionella* pneumonia, and a decrease in mortality in patients with community-acquired infection [32]. Higher prevalence of non-serotype group 1 *L. pneumophila* was previously described in immunocompromised hosts, which account for 71.8% of patients in the HAP group [24]. This factor may also contribute to a more difficult diagnosis and subsequent delay in the administration of appropriate antibiotic therapy in this group. Another factor that may be associated with a delay in diagnosis is the lower prevalence of confusion, gastrointestinal symptoms, hyponatremia, and elevation in

Table 4 Radiological characteristics of 109 patients included in the study cohort

	Chest radiograph		
	Community-acquired *Legionella* pneumonia (n = 68)	Nosocomially acquired *Legionella* pneumonia (n = 36)	p value
Bilateral opacities, n (%)	24 (35.3%)	26 (72.2%)	**< 0.001**
Pleural effusion, n (%)	28 (41.2%)	22 (61.1%)	0.08
Unilateral, n (%)	21 (30.9%)	8 (22.2%)	NS
Bilateral, n (%)	7 (10.3%)	14 (38.9%)	**0.001**
Multi-lobar involvement, n (%)	50 (73.5%)	29 (80.6%)	NS
	Chest computed tomography		
	Community-acquired *Legionella* pneumonia (n = 24)	Nosocomially acquired *Legionella* pneumonia (n = 22)	p value
Bilateral opacities, n (%)	16 (66.7%)	18 (81.8%)	NS
Pleural effusion, n (%)	17 (70.8%)	12 (54.55%)	NS
Unilateral, n (%)	7 (29.2%)	4 (18.2%)	NS
Bilateral, n (%)	10 (41.7%)	8 (36.4%)	NS
Multi-lobar involvement, n (%)	21 (87.5%)	19 (86.4%)	NS

NS nonsignificant

liver enzymes in patients with HAP. These symptoms and signs are commonly cited as clinical "clues" to *Legionella* pneumonia [33]. Patients with HAP had higher rates of leukopenia and anemia. These laboratory abnormalities were not associated with *Legionella* pneumonia in previous studies and may be explained by higher rates of immunosuppression and hematologic malignancies in the HAP group.

In our cohort, HAP more commonly involved both lungs, as demonstrated by chest radiography and CT. These findings may also contribute to a more complicated clinical course in the HAP group. Previous studies found that unilobar patchy air-space disease was the most common radiological presentation of HAP caused by *Legionella* [34]. The high proportion of immunocompromised patients in our cohort may explain this discrepancy.

In this study, we found a higher than expected mortality rates in both CAP and HAP patients, with a mean 30-day mortality rate of 26.6% as opposed to up to 10% mortality reported in most series [13, 35, 36]. However, most (69.7%) patients included in our cohort had severe pneumonia at baseline, as defined by PSI above 90. Previous studies that included patients with severe pneumonia demonstrated mortality rates comparable to those of our cohort. El-Ebiary et al. found a mortality rate of 31% and 27% for CAP and HAP, respectively, among patients with severe *Legionella* pneumonia admitted to ICU [15]. Other reports have shown variable results

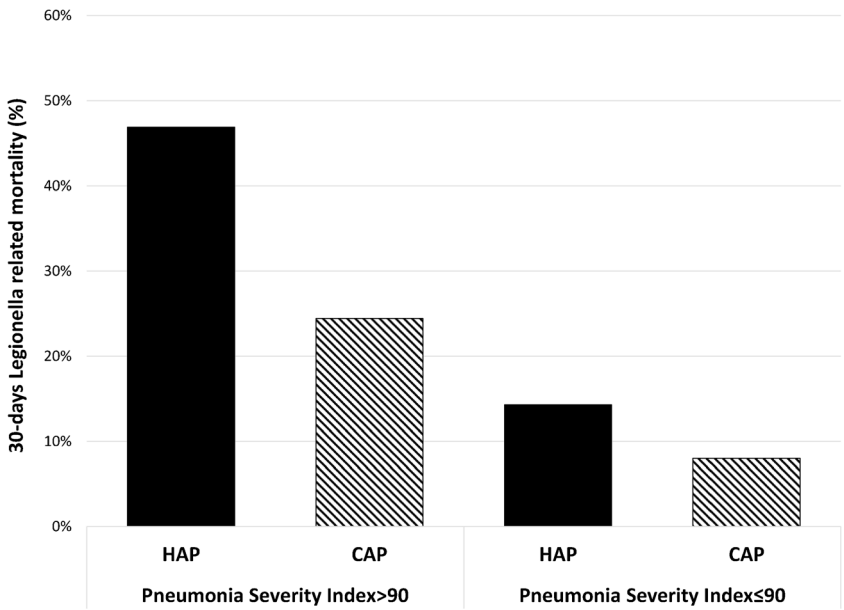

Fig. 1 The relationships between PSI, infection source (community vs. nosocomial), and 30-day *Legionella*-related mortality. PSI, pneumonia severity index; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia

ranging from 17% to as much as 47% [12, 37, 38]. A relatively large proportion of immunocompromised patients in both groups (47.1% and 71.8% in CAP and HAP groups, respectively) may also contribute to high mortality rates.

RHCC is a tertiary referral center that harbors the only bone marrow and stem cell transplantation unit and the largest oncology division in northern Israel. Therefore, the number of immunocompromised patients in our institute may be higher than those in other hospitals, reflecting the epidemiology of referral tertiary-level care hospitals. Our results may therefore not be generalizable to primary care hospitals.

Our study has some additional limitations. First, it is a retrospective study and involved only a single center. Second, the cohort was small with only 109 patients included over 7 years. The small cohort size may limit the generalization of our findings. Third, we did not have information regarding the specific serotype of each *Legionella* infection diagnosed by methods other than urine antigen. Fourth, we used PSI to compare the severity of CAP and HAP. However, PSI was developed to assess the severity of CAP and its accuracy in the assessment of HAP was not widely validated [39]. Fifth, some of the patients included in the CAP group could have acquired the infection in other healthcare facilities, before admission.

In conclusion, we found that among patients with *Legionella* pneumonia, nosocomial source of infection is independently associated with increased 30-day mortality. Our study provides some important insights into possible explanations for this excess mortality. A high index of suspicion, infection control measures in healthcare institutions, prompt recognition of outbreaks, and administration of empirical treatment to vulnerable populations may improve the outcomes of this disease. Taking into account the high mortality rate, clinicians may consider testing for *Legionella* spp. and initiating empiric anti-*Legionella* treatment in all the patients with HAP admitted to intensive care units or not responding to initial therapy with beta-lactam antibiotics. However, further prospective interventional research is required.

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Code availability Not applicable.

Authors' contributions AD conceived the idea for the study, designed the study, collected and analyzed the data, drafted the manuscript, and approved the final manuscript as submitted; DE conceived the idea for the study, designed the study, collected and analyzed the data, performed the statistical analysis drafted the manuscript, and approved the final manuscript as submitted and contributed equally as first author; AhM collected and analyzed the data, critically reviewed the manuscript, and approved the final manuscript as submitted; JN collected and analyzed the data, drafted the manuscript, and approved the final manuscript as submitted; YG conceived the idea for the study, designed the study, critically reviewed the final version of the manuscript, and approved the final manuscript as submitted; AN conceived the idea for the study, designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted; AM conceived the idea for the study, designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval The study was approved by the Institutional Review Board at Rambam Health Care Campus (approval number RMB-0593-19).

Consent to participate The need for written informed consent was waived due to the retrospective study design.

Consent for publication None.

Conflict of interest All authors report no conflicts of interest relevant to this article.

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