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Committee Report

Usefulness of the Legionella Score for differentiating from COVID-19 pneumonia to legionella pneumonia☆

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ABSTRACT

Legionella pneumophila is a major causative pathogen of community-acquired pneumonia (CAP), but recently the novel coronavirus disease 2019 (COVID-19) became the most common causative pathogen of CAP. Because L. *pneumophila* CAP is clinically distinct from bacterial CAPs, the Japan Society for Chemotherapy (JSC) developed a simple scoring system, the Legionella Score, using six parameters for the presumptive diagnosis of *L. pneumophila* pneumonia. We investigated the clinical and laboratory differences of *L. pneumophila* CAP and COVID-19 CAP and validated the Legionella Score in both CAP groups. We analyzed 102 patients with *L. pneumophila* CAP and 956 patients with COVID-19 CAP. Dyspnea and psychiatric symptoms were more frequently observed and cough was less frequently observed in patients with *L. pneumophila* CAP than those with COVID-19 CAP. Loss of taste and anosmia were observed in patients with COVID-19 CAP but not observed in those with *L. pneumophila* CAP. C-reactive protein and lactate dehydrogenase levels in *L. pneumophila* CAP group were significantly higher than in the COVID-19 CAP group. In contrast, sodium level in the *L. pneumophila* CAP group was significantly lower than in the COVID-19 CAP group. The median Legionella Score was significantly higher in the *L. pneumophila* CAP group than the COVID-19 CAP group (score 4 vs 2, $p < 0.001$). Our results demonstrated that the JSC Legionella Score had good diagnostic ability during the COVID-19 pandemic. However, physicians should consider COVID-19 CAP when loss of taste and/or anosmia are observed regardless of the Legionella Score.

1. Introduction

Legionella pneumonia accounts for 2–9% of community-acquired pneumonia (CAP) cases and is associated with high morbidity, as shown by the high proportion of patients requiring intensive care unit admission [1–3]. *Legionella pneumophila* was identified as the causative pathogen in more than 80% of *Legionella* pneumonia cases. Although the diagnosis of *L. pneumophila* pneumonia is dependent on a urinary antigen test, high-quality studies showed low sensitivity for this test [4]. Because L. *pneumophila* pneumonia has several clinical features [5], clinical scoring systems for the presumptive diagnosis of *Legionella* pneumonia have been proposed [6–11]. The Japan Society for Chemotherapy (JSC) Legionella study group also developed a scoring system, the Legionella Score, to distinguish patients with *L. pneumophila* CAP and other types of CAP [12].

The novel coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the severe acute respiratory syndrome coronavirus

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List of abbreviations

CAP	community-acquired pneumonia
CRP	C-reactive protein
COVID-19	Coronavirus disease 2019
JCS	Japan Society for Chemotherapy
JRS	Japanese Respiratory Society
LDH	lactate dehydrogenase
PCR	polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

2 (SARS-CoV-2) [13]. Since December 2019, more than 500 million infected cases have been reported worldwide. At present, SARS-CoV-2 has become the most common causative pathogen of CAP. In the previous study, we evaluated the Legionella Score using the major CAP causative pathogens, *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* [5]. Our results demonstrated the median Legionella Score was significantly higher in the *L. pneumophila* pneumonia group than the *S. pneumoniae* CAP group and *M. pneumoniae* CAP group. The JSC Legionella study group need to continue to verify scoring system to distinguish patients with *L. pneumophila* CAP and other types of CAP.

In the present study, we investigated the clinical and laboratory differences of *L. pneumophila* CAP and COVID-19 CAP. In addition, the Legionella Score proposed by the JSC Legionella study group was further validated in an independent CAP cohort that included both *L. pneumophila* and COVID-19.

2. Patients and methods

2.1. Patients

All adult patients with CAP [14] who visited Kansai Medical University Hospital, Kansai Medical University Medical Center, Kansai Medical University Kori Hospital, Kansai Medical University Kuzuha Hospital, or Kansai Medical University Temmabashi General Clinic, Osaka, Japan from January 2012 to December 2021, were enrolled in this study.

L. pneumophila was considered to be the definitive causative agent with a positive urinary antigen test, culture, and/or real-time polymerase chain reaction (PCR) and/or a four-fold rise in antibody titer level between paired sera. COVID-19 was considered to be the definitive causative agent with a positive reverse transcription-PCR result from sputum or nasopharyngeal swab specimens in accordance with the protocol recommended by the National Institute of Infectious Diseases, Japan.

The severity of pneumonia was evaluated using predictive rules via the A-DROP system proposed by the Japanese Respiratory Society (JRS) CAP guidelines [14]. Patients were stratified into four severity classes: 0 point = mild, 1 or 2 points = moderate, 3 points = severe and 4 or 5 points = extremely severe. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Kansai Medical University (approval number 2020319).

2.2. Legionella Score

The JSC developed a simple *Legionella* diagnostic score using 176 patients with *Legionella* pneumonia and 419 patients with non-*Legionella* pneumonia [12]. The JSC extracted the six parameters as the Legionella Score; being male, absence of cough, having dyspnea, elevated C-reactive protein (CRP) level (≥18 mg/dL), high lactate dehydrogenase (LDH) level (≥260 U/L), and low sodium (Na) level (<134 mmol/L).

Table 1
Background, clinical symptoms and laboratory findings in patients with *Legionella pneumophila* pneumonia and COVID-19 pneumonia.

Variables	*Legionella pneumophila*	COVID-19	p-value
No. of patients	102	956	
Median age (IQR), years	67 (55–70)	56 (42–70)	<0.001
No. of males/females	90/12	599/357	<0.001
No. (%) of patients with comorbid illnesses			
Chronic lung disease	23 (22.5)	107 (11.2)	0.002
Diabetes mellitus	20 (19.6)	167 (17.5)	0.586
Chronic heart disease	7 (6.9)	45 (4.7)	0.333
Chronic renal disease	6 (5.9)	28 (2.9)	0.131
Cerebrovascular disease	6 (5.9)	26 (2.7)	0.116
Chronic liver disease	4 (3.9)	24 (2.5)	0.337
Neoplastic disease	2 (2.0)	30 (3.1)	0.762
Autoimmune disease	2 (2.0)	23 (2.4)	>0.999
No. (%) of patients with the following clinical signs and symptoms			
Dyspnea	63 (61.8)	293 (30.6)	<0.001
Sputum production	51 (50.0)	126 (13.2)	<0.001
Cough	41 (40.2)	604 (63.2)	<0.001
Psychiatric symptoms	38 (37.3)	18 (1.9)	<0.001
Gastrointestinal symptoms	14 (13.7)	104 (10.9)	0.407
Headache	12 (11.8)	121 (12.7)	0.876
Chest pain	8 (7.8)	27 (2.8)	0.015
Loss of taste	0	184 (19.2)	<0.001
Anosmia	0	167 (17.5)	<0.001
Laboratory findings, median (IQR)			
White blood cell count,/μL	11,300 (9200–14,100)	5200 (4200–6700)	<0.001
C-reactive protein, mg/dL	27.1 (22.3–33.1)	4.4 (1.6–9.3)	<0.001
Aspartate aminotransferase, U/L	62 (37–128)	34 (23–52)	<0.001
Alanine aminotransferase, U/L	47 (28–82)	26 (18–43)	<0.001
Lactate dehydrogenase (U/L)	326 (249–441)	267 (200–405)	<0.001
Sodium (mmol/L)	133 (131–138)	136 (135–139)	<0.001
No. (%) of patients with each pneumonia severity score			
Mild to moderate (0–2 points)	79 (77.5)	865 (90.5)	<0.001
Severe (3 points)	20 (19.6)	76 (7.9)	<0.001
Extremely severe (4 or 5 points)	3 (2.9)	15 (1.6)	0.406

*IQRs, interquartile ranges (IQRs).

2.3. Statistical analysis

Discrete variables are expressed as counts (percentages) and continuous variables as medians and interquartile ranges (IQRs). Frequencies were compared using Fisher's exact test. Betweengroup comparisons of normally distributed data were performed using Student's *t*-test. Skewed data were compared using the Mann–Whitney *U* test.

3. Results

3.1. Patient characteristics

The patients who fulfilled the diagnostic criteria for CAP caused by *L. pneumophila* or SARS-CoV-2 without any evidence of other causative pathogens formed the groups for comparison of the clinical presentation. We analyzed the 102 patients with *L. pneumophila* pneumonia and 956 patients with COVID-19 pneumonia. Among 102 patients with *L. pneumophila* CAP, 89 patients were urinary antigen test positive, 12 patients were culture positive, 26 patients were PCR positive, and 10 patients demonstrated a four-fold antibody seroconversion. During the study period, there were five waves of COVID-19 in Japan, the first to third waves involved the conventional strain, the fourth wave with lineage B.1.1.7 (Alpha variant), and the fifth wave with lineage B.1.617 (Delta variant). Of 956 patients with COVID-19 CAP, 422 had the conventional strain, 260 had the Alpha variant, and 274 had the Delta variant.

Table 2
Legionella score in patients with *Legionella pneumophila* pneumonia and COVID-19 pneumonia.

Variables	*Legionella pneumophila*	COVID-19				p-value
		Conventional Strain	Alpha variant	Delta variant	Total	
No. of patients	102	422	260	274	956	
Legionella score						
Score 0	0	52	21	34	107	
Score 1	0	114	44	93	251	
Score 2	4	147	76	86	309	
Score 3	10	62	79	37	178	
Score 4	37	34	34	17	85	
Score 5	37	12	6	6	24	
Score 6	14	1	0	1	2	
Median (IQR)	4 (4–5)	2 (1–3)	2 (1.75–3)	2 (1–2)	2 (1–3)	<0.001

*IQR, interquartile ranges (IQRs).
P value: 102 *Legionella pneumophila* pneumonia versus 956 COVID-19 pneumonia.

Table 3
Background, clinical symptoms and laboratory findings in patients with *Legionella pneumophila* pneumonia and age- and gender-matched COVID-19 pneumonia.

Variables	*Legionella pneumophila*	COVID-19	p-value
No. of patients	102	102	
Median age (IQR), years	67 (55–70)	67 (55–70)	>0.999
No. of males/females	90/12	90/12	>0.999
No. (%) of patients with comorbid illnesses			
Chronic lung disease	23 (22.5)	13 (12.7)	0.097
Diabetes mellitus	20 (19.6)	21 (20.6)	>0.999
Chronic heart disease	7 (6.9)	8 (7.8)	>0.999
Chronic renal disease	6 (5.9)	8 (7.8)	0.783
Cerebrovascular disease	6 (5.9)	8 (7.8)	0.783
Chronic liver disease	4 (3.9)	4 (3.9)	>0.999
Neoplastic disease	2 (2.0)	5 (4.9)	0.445
Autoimmune disease	2 (2.0)	3 (2.9)	>0.999
No. (%) of patients with the following clinical signs and symptoms			
Dyspnea	63 (61.8)	29 (28.4)	<0.001
Sputum production	51 (50.0)	13 (12.7)	<0.001
Cough	41 (40.2)	59 (57.8)	0.017
Psychiatric symptoms	38 (37.3)	2 (2.0)	<0.001
Gastrointestinal symptoms	14 (13.7)	13 (12.7)	>0.999
Headache	12 (11.8)	10 (9.8)	0.822
Chest pain	8 (7.8)	2 (2.0)	0.101
Loss of taste	0	14 (13.7)	<0.001
Anosmia	0	12 (11.8)	<0.001
Laboratory findings, median (IQR)			
White blood cell count,/μL	11,300 (9200–14,100)	5300 (4400–7100)	<0.001
C-reactive protein, mg/dL	27.1 (22.3–33.1)	3.6 (1.3–7.7)	<0.001
Aspartate aminotransferase, U/L	62 (37–128)	38 (26–61)	<0.001
Alanine aminotransferase, U/L	47 (28–82)	26 (18–42)	<0.001
Lactate dehydrogenase (U/L)	326 (249–441)	259 (196–385)	<0.001
Sodium (mmol/L)	133 (131–138)	136 (134–139)	<0.001
No. (%) of patients with each pneumonia severity score			
Mild to moderate (0–2 points)	79 (77.5)	84 (82.4)	0.485
Severe (3 points)	20 (19.6)	15 (14.7)	0.458
Extremely severe (4 or 5 points)	3 (2.9)	3 (2.9)	>0.999

*IQRs, interquartile ranges (IQRs).

3.2. Differences between Legionella pneumophila and COVID-19 CAP groups

Background, clinical symptoms, and laboratory findings in patients with *Legionella pneumophila* pneumonia and COVID-19 pneumonia were shown in Table 1. The median age and male frequency were significantly higher in patients with *L. pneumophila* CAP than those with COVID-19 CAP. Among comorbid illnesses, the frequency of chronic lung disease was significantly higher in patients with *L. pneumophila* CAP than those with COVID-19 CAP.

Although dyspnea, sputum production, and psychosis were observed more frequently in patients with *L. pneumophila* CAP than those with COVID-19 CAP, cough was observed less frequently in patients with *L. pneumophila* CAP than those with COVID-19 CAP. Loss of taste and anosmia were observed in patients with COVID-19 CAP, but not observed in those with *L. pneumophila* CAP. However, we just confirmed symptoms commonly seen with pneumonia in patients with *L. pneumophila* CAP. We did not interview directly with or without loss of taste and anosmia in patients with *L. pneumophila* CAP.

The median CRP and LDH levels in the *L. pneumophila* CAP group were 27.1 mg/dL and 326 U/L, respectively, which were significantly higher than in the COVID-19 CAP group. Median Na level in the *L. pneumophila* CAP group was 133 mmol/L which was significantly lower than in the COVID-19 CAP group.

3.3. Evaluation of the Legionella Score

Table 2 shows the number of patients in each Legionella Score in both CAP groups. Among COVID-19 cases median Legionella Score was identical the among conventional strain, Alpha variant and Delta variant. The median Legionella Score was significantly higher in the *L. pneumophila* CAP group than the COVID-19 CAP group (score 4 vs 2, $p < 0.001$). When the cutoff was score $\geq$4, the diagnostic sensitivity and specificity for presumptive diagnosis of *L. pneumophila* CAP were 86.3% and 88.4%, respectively.

3.4. Differences between two age- and gender-matched CAP groups

Background, clinical symptoms, and laboratory findings in patients with *Legionella pneumophila* pneumonia and age- and gender-matched patients with COVID-19 pneumonia are shown in Table 3. Dyspnea, sputum production, and psychosis were observed more frequently and cough was observed less frequently in patients with *L. pneumophila* CAP than those with COVID-19 CAP. The median CRP, LDH, and Na levels were identical between the age- and gender-matched patients and non-matched patients with COVID-19 CAP. The median Legionella Score was still 2 (IQR 1–3) in the age- and gender-matched patients with COVID-19 CAP.

3.5. Differences between non-severe and severe COVID-19 CAP groups

To clarify the usefulness of Legionella Score among the pneumonia severity, we analyzed patients with COVID-19 pneumonia between non-

Table 4
Background, clinical symptoms and laboratory findings in patients with non-severe and severe COVID-19 pneumonia.

Variables	Non-severe	Severe	p-value
No. of patients	865	91	
Median age (IQR), years	53 (40–67)	73 (77–80)	<0.001
No. of males/females	534/331	65/26	0.087
No. (%) of patients with comorbid illnesses			
Chronic lung disease	95 (11.0)	12 (13.2)	0.488
Diabetes mellitus	133 (15.4)	34 (37.4)	<0.001
Chronic heart disease	31 (3.6)	14 (15.4)	<0.001
Chronic renal disease	23 (2.7)	5 (5.5)	0.177
Cerebrovascular disease	19 (2.2)	7 (7.7)	0.008
Chronic liver disease	23 (2.7)	1 (1.1)	0.720
Neoplastic disease	25 (2.9)	5 (5.5)	0.196
Autoimmune disease	21 (2.4)	2 (2.2)	>0.999
No. (%) of patients with the following clinical signs and symptoms			
Dyspnea	251 (29.0)	42 (46.2)	0.001
Sputum production	114 (13.2)	12 (13.2)	>0.999
Cough	564 (65.2)	40 (44.0)	<0.001
Psychiatric symptoms	16 (1.8)	2 (2.2)	0.686
Gastrointestinal symptoms	96 (11.1)	8 (8.8)	0.598
Headache	115 (13.3)	6 (6.6)	0.167
Chest pain	27 (3.1)	0	0.101
Loss of taste	180 (20.8)	4 (4.4)	<0.001
Anosmia	163 (18.8)	4 (4.4)	<0.001
Laboratory findings, median (IQR)			
White blood cell count,/μL	5100 (4200–6500)	6500 (4950–8250)	0.239
C-reactive protein, mg/dL	4.0 (1.5–8.4)	10.0 (5.4–14.5)	0.007
Aspartate aminotransferase, U/L	33 (23–50)	49 (37–73)	<0.001
Alanine aminotransferase, U/L	26 (18–43)	31 (20–48)	0.085
Lactate dehydrogenase (U/L)	257 (198–384)	409 (322–530)	<0.001
Sodium (mmol/L)	136 (135–139)	137 (134–140)	0.582

*IQRs, interquartile ranges (IQRs).

severe (A-DROP 0, 1, or 2 points) and severe (A-DROP 3, 4, or 5 points) groups (Table 4). The median age was significantly higher in patients with severe group than those with non-severe group. Among comorbid illnesses, the frequency of diabetes mellitus, chronic heart disease, and cerebrovascular disease were significantly higher in patients with severe group than those with non-severe group.

Cough, loss of taste, and anosmia were observed more frequently and dyspnea was observed less frequently in patients with non-severe group than those with severe group. The median CRP and LDH levels in the severe group were significantly higher than in the non-severe group. Na level were identical between the two groups. The median Legionella Score was significantly higher in the severe group with 3 (IQR 2–3) than the non-severe group with 2 (IQR 1–3) (Table 5).

4. Discussion

The JRS CAP guidelines have been recommended as a rapid and simple scoring system based on clinical and laboratory findings for the presumptive diagnosis of atypical pneumonia [14]. However, our former study indicated that the JRS scoring system is not useful for predicting *Legionella* pneumonia [5]. Thus, the JSC developed a simple scoring system, the Legionella Score, using six parameters for the presumptive diagnosis of *L. pneumophila* pneumonia [12]. In the development cohort, the median Legionella Score was significantly higher in the *L. pneumophila* pneumonia group than the non-*L. pneumophila* pneumonia group with median score 4 in the *Legionella* CAP group, score 2 in the *S. pneumoniae* CAP group, and score 1 in the *M. pneumoniae* CAP group [5]. Subsequently, the Legionella Score was validated in an independent cohort and confirmed that Legionella Score was a useful tool for the presumptive diagnosis of *L. pneumophila* pneumonia [12]. In the present study, the median Legionella Score was significantly higher in the *L. pneumophila* CAP group than the COVID-19 CAP group (score 4 vs 2, $p < 0.001$). In the age- and gender-matched COVID-19 CAP group, the median Legionella Score was identical at 2 (IQR 1–3) as in the non-matched COVID-19 CAP group. In addition, the median Legionella Score was significantly higher in the *L. pneumophila* CAP group than the COVID-19 CAP group regardless of pneumonia severity. In contrast, the presence of loss of taste and/or anosmia was specific to the COVID-19 CAP group.

Being male, with dyspnea, and absence of cough were identified as independent predictors of *L. pneumophila* CAP in the former cohorts [5, 12]. These parameters were confirmed as independent predictors of *Legionella* CAP in other surveillance in Japan [15], but not identified in other countries [7–11]. In Japan, outbreaks due to *L. pneumophila* have been reported regularly in hot spring facilities, bathing facilities, or public bathhouses. In addition, outbreaks have been connected with the use of humidifiers contaminated with *L. pneumophila*. Thus, traditional bathing culture in Japan may be linked to these parameters.

In conclusion, our results demonstrated that *L. pneumophila* CAP was clearly different from COVID-19 CAP. Dyspnea and psychiatric symptoms were more frequently observed and cough was less frequently observed in patients with *L. pneumophila* CAP than those with COVID-19 CAP. CRP and LDH levels were markedly elevated and Na level was significantly lower in patients with *L. pneumophila* CAP. Thus, the Legionella Score shown to have good diagnostic ability during the COVID-19 pandemic. However, physicians should consider COVID-19 CAP when loss of taste and/or anosmia are observed regardless of the Legionella Score.

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Table 5
Legionella score in patients with *Legionella pneumophila* pneumonia and COVID-19 pneumonia.

Variables	*Legionella pneumophila*	COVID-19			p-value Legionella vs non-severe COVID-19	p-value Legionella vs severe COVID-19
		Non-severe	Severe	Total		
No. of patients	102	865	91	956		
Legionella score						
Score 0	0	107	0	107		
Score 1	0	247	4	251		
Score 2	4	276	33	309		
Score 3	10	145	33	178		
Score 4	37	71	14	85		
Score 5	37	18	6	24		
Score 6	14	1	1	2		
Median (IQR)	4 (4–5)	2 (1–3)	3 (2–3)	2 (1–3)	<0.001	0.022

*IQR, interquartile ranges (IQRs).

Availability of data and materials

The data will not be shared because of participant confidentiality.

Author's contributions

All the authors conceived the study, participated in its design and coordination, and collected and managed the data, including quality control. NM drafted the manuscript, and all authors contributed substantially to its revision. All the authors read and approved the final manuscript.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee at Kansai Medical University and all participating facilities. Informed consent was obtained from all individual participants in the study.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

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