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【 ORIGINAL ARTICLE 】

# A Novel Diagnostic Scoring System to Differentiate between *Legionella pneumophila* Pneumonia and *Streptococcus pneumoniae* Pneumonia

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**Abstract:**

**Objective** We investigated a novel diagnostic scoring system to differentiate *Legionella pneumophila* pneumonia from *Streptococcus pneumoniae* pneumonia.

**Methods** We retrospectively reviewed the clinical data of 62 patients with *L. pneumophila* pneumonia (L-group) and 70 patients with *S. pneumoniae* pneumonia (S-group).

**Results** The serum sodium (Na) levels tended to be lower according to the severity [age, dehydration, respiratory failure, orientation disturbance, low blood pressure (A-DROP)] score in the L-group. On a multivariate analysis, we found that four factors were independent predictive markers for inclusion in the L-group: relative bradycardia [hazard ratio (HR) 5.177, 95% confidence interval (CI): 1.072-24.993, p=0.041], lactate dehydrogenase (LDH) levels ≥292 IU/L (HR 6.804, 95% CI: 1.629-28.416, p=0.009), C-reactive protein (CRP) levels ≥21 mg/dL (HR 28.073, 95% CI: 5.654-139.462, p<0.001), and Na levels ≤137 meq/L (HR 5.828, 95% CI: 1.411-24.065, p=0.015). Furthermore, a total score [ranging from 0 to 4, the sum of the points for each factor (0 or 1)] ≥3 points indicated a higher probability of inclusion in the L-group than in the S-group. The diagnostic accuracy of a total score of 3 had a sensitivity of 36.3%, specificity of 100%, and area under the curve of 0.682 (95% CI: 0.558-0.806, p=0.004), and that of a total score of 4 had a sensitivity 27.4%, specificity of 98.2%, and area under the curve (AUC) of 0.627 (95% CI: 0.501-0.754, p=0.045). The diagnostic accuracy had low sensitivity but high specificity.

**Conclusions** We found four markers that might be useful for differentiating L-group from S-group and created a novel diagnostic scoring system.

**Key words:** *Legionella pneumophila* pneumonia, hyponatremia, diagnostic scoring system

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## Introduction

Although *Legionella pneumophila* pneumonia and *Streptococcus pneumoniae* pneumonia can both be life-threatening diseases that present as lobar pneumonia, a simple method of differentiating them has yet to be reported. Regarding clinical findings, general physicians understand that *L. pneumophila* pneumonia causes hyponatremia and/or relative bradycardia; however, the diagnostic accuracy of such findings is relatively unknown. Therefore, we retrospectively reviewed the data of *L. pneumophila* pneumonia patients to generate a simple diagnostic scoring system to differentiate it from *S. pneumoniae* pneumonia.

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## Materials and Methods

### Patients and study design

We retrospectively reviewed the medical records of patients diagnosed with *L. pneumophila* pneumonia between January 2001 and December 2016 and searched the Japanese medical literature using the database "Ichushi" (1-12). We included patients whose data were available in the literature. For comparison, we also reviewed the medical records of *S. pneumoniae* pneumonia patients during the period between January 2013 and September 2014. Patients co-infected with other pathogens were excluded from the study. This study was approved by the Ethics Board of Kyorin University.

### Definition

*L. pneumophila* pneumonia was identified based on the following: 1) a new shadow visualized on chest radiography or chest computed tomography (CT); 2) sputum culture result positive for *L. pneumophila;* 3) polymerase chain reaction result positive for *L. pneumophila;* or 4) a positive result for the legionella urinary antigen test (BinaxNOW®, Alere, Tokyo, Japan). Similarly, *S. pneumoniae* pneumonia was identified based on the following: 1) a new shadow visualized on chest radiography or chest CT; 2) sputum culture result positive for *S. pneumoniae* obtained from good sputum samples (Geckler 4 or Geckler 5); or a positive result for *S. pneumoniae* urinary antigen test (BinaxNOW®). Respiratory failure was defined as oxygen saturation measured by pulse oximetry <90% or a respiratory status indicating that oxygen supply was required. Relative bradycardia was based on the definition by Cunha (13). All data were collected at the time of admission.

### Statistical analyses

Categorical data are presented as percentages of the total or numerically, as appropriate. Statistical comparisons of nonparametric data were performed using the Mann-Whitney test or Wilcoxon's signed-rank test. Comparisons of categorical data were made using Pearson's chi-squared test. All tests were two-sided. A value of $p<0.05$ indicated statistical significance. Logistic regression modeling was used for uni- and multivariate analyses to identify predictive risk factors for *L. pneumophila* pneumonia compared with those for *S. pneumoniae* pneumonia. Receiver operating characteristic (ROC) curves were used to assess the differentiative powers of serum C-reactive protein (CRP), lactate dehydrogenase (LDH), and sodium (Na) levels. The cut-off point for the serum markers was determined as the minimum value of $[(1\text{-sensitivity})^2+(1\text{-specificity})^2]$. Data were analyzed using the SPSS version 20.0 software program for Windows (IBM Japan, Tokyo, Japan).

## Results

We found a total of 62 patients with *L. pneumophila* pneumonia (24 cases from our hospital and 38 from the literature review) and 70 patients with *S. pneumoniae* pneumonia from our hospital.

### Clinical characteristics of the patients with L. pneumophila pneumonia and S. pneumoniae pneumonia

A comparison of the data between the patients with *L. pneumophila* pneumonia (L-group) and those with *S. pneumoniae* pneumonia (S-group) groups showed that the median age was similar between the groups; however, the proportion of men was significantly higher in the L-group (Table 1) than in the S-group. The duration from the initial onset of symptoms to the first visit to a local health facility or to our hospital was significantly shorter in the L-group [median 3 days, interquartile range (IQR): 1.0-5.0, p=0.028] than in the S-group (median 3 days, IQR: 1.8-7.0). Interestingly, the body temperature and heart rate were significantly higher in the L-group (median, 38.8℃, IQR: 37.2-39.3℃, p <0.001 and median 108 beats/min, IQR: 94-120 beats/min, p <0.001, respectively) than in the S-group (median 38.0℃, IQR 37.0-38.9°C and 100 beats/min, IQR: 84-107 beats/min, respectively). The frequency of relative bradycardia was markedly higher in the L-group (44.4%, p=0.001) than in the S-group (15.6%). The age, dehydration, respiratory failure, orientation disturbance, low blood pressure (A-DROP) score proposed by the Japanese Respiratory Society [comparable result to that of CURB-65 (14)] showed similar trends in the L- and S-groups (Table 1).

### A comparison of the serum laboratory data between the L- and S-groups

Serum laboratory results showed that the white blood cell count was comparable between the L- and S-groups; however, the levels of LDH, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and CRP were significantly higher in the L-group (median 378 IU/L, IQR 299-523, p< 0.001; median 66.5 IU/L, IQR 36-132, p<0.001; median 43.5 IU/L, IQR 23.5-75.3, p<0.001; median 27.4 mg/dL, IQR 22.1-38.2, p<0.001, respectively) than in the S-group (median 224 IU/L, IQR 197-283; median 23 IU/L, IQR 16-33.5; median 15 IU/L, IQR 12-25; median 7.8 mg/dL, IQR 2.9-14.9, respectively) (Table 2). The serum sodium levels were significantly lower in the L-group (median 135.5 meq/L, IQR 132-139, p<0.001) than in the S-group (median 139 meq/L, IQR 137-141).

### Distribution of serum sodium levels in L. pneumophila pneumonia categorized by A-DROP score

The serum sodium levels seemed to be linked to the A-DROP score (Fig. 1). As shown in Fig. 1, the sodium levels in patients with an A-DROP score of 4 (median 140 meq/L, IQR 138.5-144.3) were significantly higher than those in pa-

**Table 1. Demographical and Clinical Details of Patients with *Legionella Pneumophila* Pneumonia and *Streptococcus Pneumoniae* Pneumonia.**

| | *Legionella pneumophila* pneumonia (n=62) | *Streptococcus pneumoniae* pneumonia (n=70) | p value |
|---|---|---|---|
| Age (years) | 68.5 (55-80.5) | 72.5 (43.8-83.0) | 0.473 |
| Sex (M/F) | 54/8 | 38/32 | <0.001 |
| Underlying respiratory diseases | 12/28 (42.9%) | 31/43 (72.1%) | 1.0 |
| Inpatients | 61 (98.4%) | 34 (48.6%) | <0.001 |
| Smoker | 24/28 (85.7%) | 31/45 (68.9%) | 0.162 |
| Initial onset to first visit to a local or our hospital (days) | 3.0 (1.0-5.0) | 3.5 (1.8-7.0) | 0.028 |
| Body temperature (°C) | 38.8 (37.2-39.3) | 38.0 (37.0-38.9) | <0.001 |
| Heart rate | 108 (94-120) | 100 (84-107) | <0.001 |
| Relative bradycardia | 24/54 (44.4%) | 10/64 (15.6%) | 0.001 |
| Respiratory failure# | 11/45 (24.45) | 22/54 (40.7%) | 0.133 |
| Diagnostic methods | | | |
| Positive for urinary antigen test | 58/60 (96.7%) | 25/47 (53.2%) | <0.001 |
| Culture positive | 8/21 (38.1%) | 70 (100%) | <0.001 |
| PCR positive | 5/6 (83.3%) | NA | |
| A-DROP* | | | |
| 0 | 11 (20%) | 20 (35.7%) | 0.09 |
| 1 | 18 (32.7%) | 14 (25%) | 0.407 |
| 2 | 13 (23.6%) | 6 (10.7%) | 0.082 |
| 3 | 9 (16.4%) | 12 (21.4%) | 0.629 |
| 4 | 3 (5.5%) | 3 (5.4%) | 1.0 |
| 5 | 1 (1.8%) | 1 (1.8%) | 1.0 |

All data are expressed as median (25th-75th percentile) or number (%).

*A-DROP score was available in only 55 patients with *Legionella pneumophila* pneumonia and 56 patients with *S. pneumoniae* pneumonia

#Definition of respiratory failure is $SpO_2$ less than 90% or respiratory status required oxygen supply

PCR: polymerase chain reaction, A-DROP: age, dehydration, respiratory failure, orientation disturbance, low blood pressure, NA: not available

**Table 2. Comparison of the Serum Laboratory Results between the Patients with *Legionella Pneumophila* Pneumonia and *S. Pneumoniae* Pneumonia.**

| | *Legionella pneumophila* pneumonia (n=62) | *Streptococcus pneumoniae* pneumonia (n=70) | p value |
|---|---|---|---|
| WBC ($\times 10^3/\mu L$) | 10,600 (7,600-13,800) | 10,900 (8,350-14,525) | 0.662 |
| LDH (IU/L) | 378 (299-523) | 224 (197-283) | <0.001 |
| AST (IU/L) | 66.5 (36-132) | 23 (16-33.5) | <0.001 |
| ALT (IU/L) | 43.5 (23.5-75.3) | 15 (12-25) | <0.001 |
| Na (meq/L) | 135.5 (132-139) | 139 (137-141) | <0.001 |
| CRP (mg/dL) | 27.4 (22.1-38.2) | 7.8 (2.9-14.9) | <0.001 |

All data are expressed as median (25th-75th percentile).

WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, LDH: lactate dehydrogenase

tients with a score of 0 (median 138 meq/L, IQR 133-139.5, p=0.05), 1 (median 135 meq/L, IQR 132-138, p=0.002), or 3 (median 137 meq/L, IQR 134-140, p=0.043), but not in patients with a score of 2 (median 137 meq/L, IQR 131-140, p=0.074) or 5 (median 143.5 meq/L, p=0.180).

When patients with *L. pneumophila* pneumonia were divided into groups according to their A-DROP scores (1, 2, 3, and 4), we found that the serum sodium levels were significantly lower in the A-DROP <3 group (median 136.5 meq/L, IQR 133-139, p=0.026) than in the A-DROP ≥3 group (median 139 meq/L, IQR 136-140.5) (Fig. 2). The trend was similar for the A-DROP <4 group (median 137 meq/L, IQR 133-139, p=0.001) versus the A-DROP ≥4 group (median 141 meq/L, IQR 139-143) (Fig. 2), implying that the serum sodium levels were likely to be lower in patients with lower A-DROP scores [mild to moderate severe community-acquired pneumonia (CAP)].

### *Differentiation of L. pneumophila pneumonia from S. pneumoniae pneumonia*

The most appropriate cut-off levels (sensitivity, specificity) for differentiation between the L-group and S-group were 21.5 mg/dL for CRP (78.6%, 91%), 292 IU/L for LDH (71.8%, 83.9%), and 137.5 meq/L for sodium (72.6%, 77.6%) (Fig. 3). Of these 3 factors, a univariate analysis showed that the cut-off level for serum CRP of 21.5 mg/dL had the highest power to predict *L. pneumophila* pneumonia [hazard ratio (HR) 36.667, 95% confidence interval (CI): 12.001-112.032, p<0.001] (Table 3). Diagnostic accuracy was also demonstrated by other predictive markers, such as the serum sodium levels ≤137 meq/L (HR 12.706, 95% CI: 5.267-30.562, p<0.001), LDH levels ≥292 IU/L (HR 11.667, 95% CI: 4.475-30.417, p<0.001), and relative bradycardia (HR 4.320, 95% CI: 1.824-10.231, p<0.001) (Table 3).

Based on the multivariate analysis, the above 4 predictive factors (relative bradycardia, LDH ≥292 IU/L, CRP ≥21 mg/dL, and Na ≤137 meq/L) seem to be reliable markers for differentiating between *L. pneumophila* pneumonia and *S. pneumoniae* pneumonia (Table 4), even in the setting of A-DROP <4 (Table 5). All parameters showed strong, independent associations with *L. pneumophila* pneumonia.

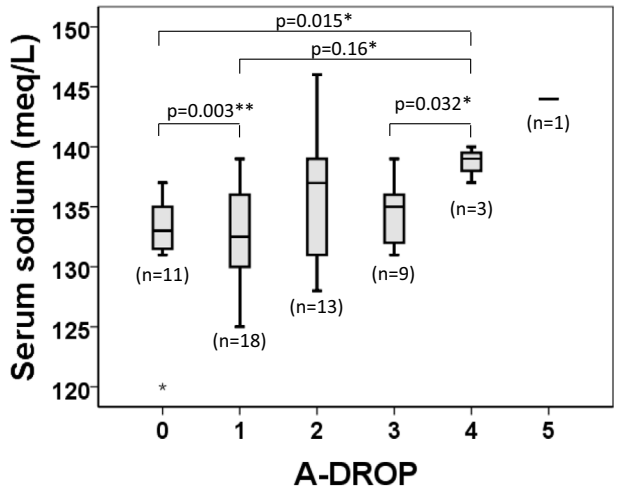


**Figure 1. The distribution of the serum sodium levels in *Legionella pneumophila* pneumonia categorized by the A-DROP score. All data are expressed as the median (25th-75th percentile). A-DROP: age, dehydration, respiratory failure, orientation disturbance, low blood pressure**

### *The diagnostic accuracy of the total score for differentiating L. pneumophila pneumonia from S. pneumoniae pneumonia*

To estimate the probability of *L. pneumophila* pneumonia, we assigned scores of 0 or 1 for serum LDH levels ≥292 IU/L, serum sodium levels ≤137 meq/L, serum CRP levels ≥21 mg/dL, and relative bradycardia, with a total score rang-

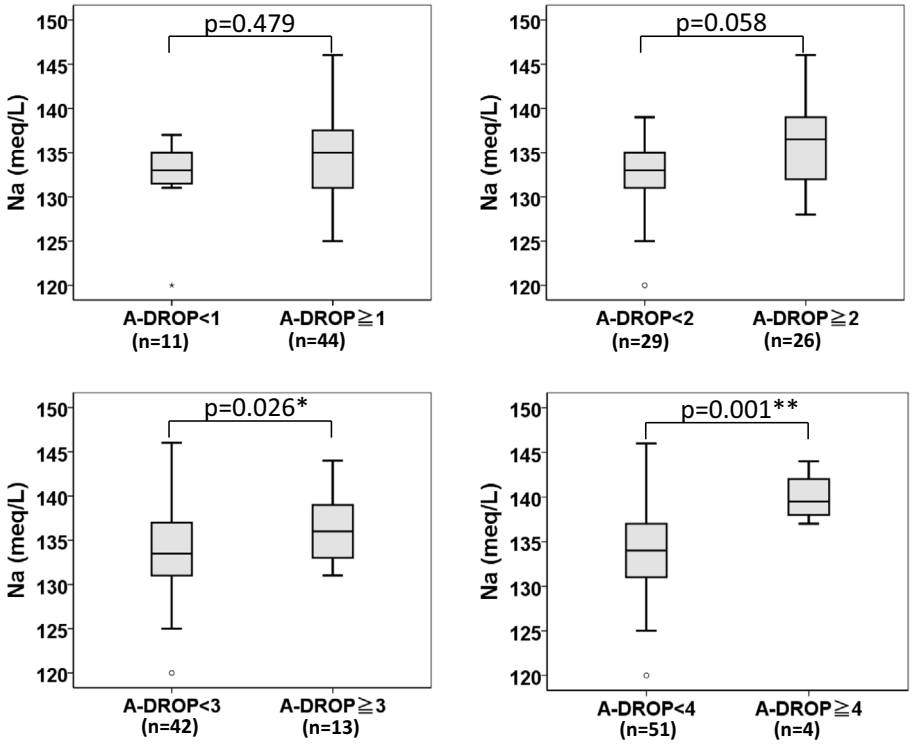


**Figure 2. A comparison of the serum sodium levels in groups categorized by the A-DROP score. A-DROP<1 means A-DROP 0. A-DROP<2 means A-DROP ≤0 plus A-DROP 1. A-DROP<3 means A-DROP ≤0 plus A-DROP 1 plus A-DROP 2. A-DROP<4 means A-DROP ≤0 plus A-DROP 1 plus A-DROP 2 plus A-DROP 3. All data are expressed as the median (25th-75th percentile). A-DROP: age, dehydration, respiratory failure, orientation disturbance, low blood pressure**

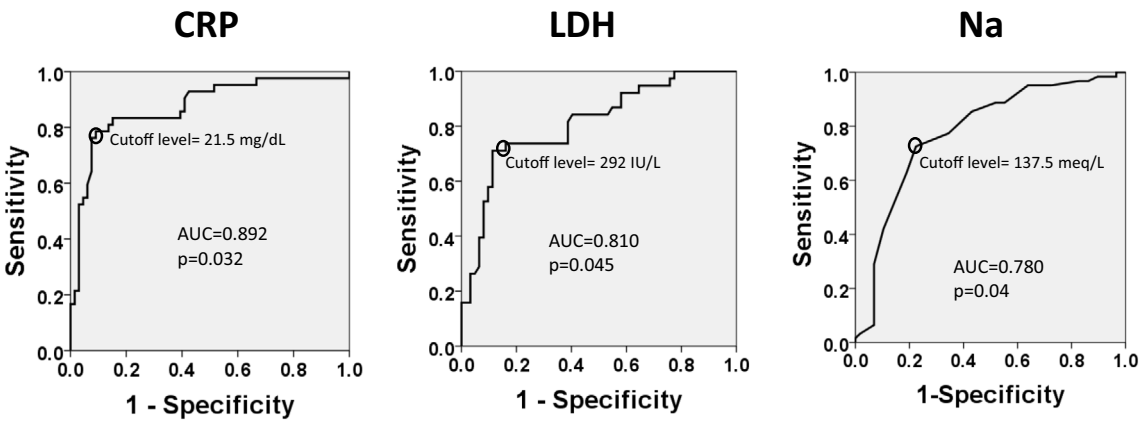


**Figure 3.** **Differentiating *Legionella pneumophila* pneumonia from *Streptococcus pneumoniae* pneumonia using the serum CRP, LDH, and sodium levels. AUC: area under the curve.**

**Table 3.** **Univariate Analysis of Discrimination between *Legionella Pneumophila* Pneumonia and *S. Pneumoniae* Pneumonia.**

| | Hazard ratio | 95% CI | p value |
|---|---|---|---|
| Age | 1.002 | 0.981-1.022 | 0.881 |
| Sex | 5.684 | 2.360-13.689 | <0.001 |
| Smoker | 2.71 | 0.790-9.292 | 0.113 |
| Underlying respiratory diseases | 0.944 | 0.390-2.285 | 0.898 |
| Initial onset to visit to a local or our hospital (days) | 1.163 | 1.007-1.344 | 0.04 |
| Respiratory failure* | 0.471 | 0.197-1.123 | 0.089 |
| WBC | 1 | 1.0-1.0 | 0.447 |
| LDH | 0.992 | 0.988-0.996 | <0.001 |
| LDH ≥292 IU/L | 11.667 | 4.475-30.417 | <0.001 |
| Na | 1.272 | 1.144-1.415 | <0.001 |
| Na ≤137 meq/L | 12.706 | 5.267-30.652 | <0.001 |
| CRP | 0.85 | 0.802-0.901 | <0.001 |
| CRP ≥21 mg/dL | 36.667 | 12.001-112.032 | <0.001 |
| Heart rate | 0.977 | 0.957-0.997 | 0.026 |
| Body temperature | 0.664 | 0.488-0.902 | 0.009 |
| Relative bradycardia | 4.320 | 1.824-10.231 | 0.001 |

[#]Definition of respiratory failure is $SpO_2$ less than 90% or respiratory status required oxygen supply
WBC: white blood cell count, CRP: C-reactive protein, LDH: lactate dehydrogenase

**Table 4.** **Multivariate Analysis of Discrimination between *Legionella Pneumophila* Pneumonia and *S. Pneumoniae* Pneumonia.**

| | HR | 95% CI | p value |
|---|---|---|---|
| Relative bradycardia | 5.177 | 1.072-24.993 | 0.041 |
| LDH ≥292 (IU/L) | 6.804 | 1.629-28.416 | 0.009 |
| CRP ≥21 (mg/dL) | 28.073 | 5.651-139.462 | <0.001 |
| Na ≤137 (meq/L) | 5.828 | 1.411-24.065 | 0.015 |

CRP: C-reactive protein, HR: hazard ratio, LDH: lactate dehydrogenase

**Table 5.** **Multivariate Analysis of Discrimination between *Legionella Pneumophila* Pneumonia and *S. Pneumoniae* Pneumonia, with Specific Reference to the Patients with A-DROP 0, 1, 2, and 3.**

| | HR | 95% CI | p value |
|---|---|---|---|
| Relative bradycardia | 5.797 | 1.103-30.474 | 0.038 |
| LDH ≥292 (IU/L) | 6.462 | 1.445-28.902 | 0.015 |
| CRP ≥21 (mg/dL) | 22.243 | 4.132-119.742 | <0.001 |
| Na ≤137 (meq/L) | 4.812 | 1.059-21.868 | 0.042 |

CRP: C-reactive protein, HR: Hazard ratio, LDH: lactate dehydrogenase

ing from 0 to 4. The proportion of patients with *L. pneumophila* pneumonia compared to *S. pneumoniae* pneumonia for each total score (diagnostic score) increased markedly at 3 and 4 points (Fig. 4). The differentiative accuracy of the total score proved to be promising when the total score was 3 points [sensitivity 36.3%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 72.7%, and AUC 0.682; 95% CI: 0.558-0.806, p=0.004] or 4 points (sensitivity 27.35%, specificity 98.2%, PPV 90%, NPV 69.6%, and AUC 0.627; 95% CI: 0.501-0.754, p=

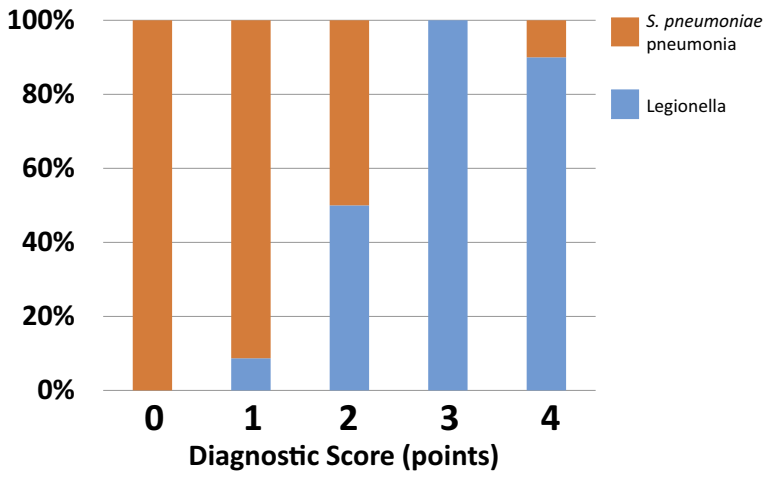


**Figure 4.** **Patients with *Legionella pneumophila* pneumonia and *Streptococcus. pneumoniae* pneumonia according to the diagnostic score. The numbers in the boxes represent the total numbers of patients.**

**Table 6.** **Diagnostic Accuracy of the Total Score in Differentiating *Legionella Pneumophila* Pneumonia from *S. Pneumoniae* Pneumonia.**

| Total score | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUC | 95% CI | p value |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 57.1 | 0 | 49.2 | 0.286 | 0.182-0.389 | 0.001 |
| 1 | 6.1 | 61.1 | 8.7 | 51.6 | 0.336 | 0.223-0.449 | 0.011 |
| 2 | 30.3 | 81.5 | 50 | 65.7 | 0.559 | 0.432-0.686 | 0.301 |
| 3 | 36.3 | 100 | 100 | 72.7 | 0.682 | 0.558-0.806 | 0.004 |
| 4 | 27.3 | 98.2 | 90 | 69.6 | 0.627 | 0.501-0.754 | 0.045 |

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value

**Table 7.** **Specifications of Different Clinical Models.**

| Model | | All cases* | Especially focused on the A-DROP<4** |
|---|---|---|---|
| | Independent variables | AUC (95% CI) | AUC (95% CI) |
| Model 1 | Relative bradycardia | 0.653 (0.532-0.775, p=0.015) | 0.664 (0.535-0.794, p=0.017) |
| Model 2 | LDH ≥292 (IU/L) | 0.773 (0.669-0.878, p<0.001) | 0.786 (0.676-0.896, p<0.001) |
| Model 3 | CRP ≥21 (mg/dL) | 0.828 (0.731-0.925, p<0.001) | 0.827 (0.722-0.931, p<0.001) |
| Model 4 | Na ≤137 (meq/L) | 0.761 (0.656-0.865, p<0.001) | 0.752 (0.637-0.867, p<0.001) |
| Model 5 | LDH ≥292 (IU/L) and CRP ≥21 (mg/dL) | 0.795 (0.683-0.907, p<0.001) | 0.791 (0.673-0.908, p<0.001) |
| Model 6 | LDH ≥292 (IU/L) and Na ≤137 (meq/L) | 0.697 (0.570-0.825, p=0.003) | 0.708 (0.575-0.840, p=0.004) |
| Model 7 | LDH ≥292 (IU/L) and relative bradycardia | 0.797 (0.684-0.910, p<0.001) | 0.797 (0.679-0.915, p<0.001) |
| Model 8 | CRP ≥21 (mg/dL) and Na ≤137 (meq/L) | 0.664 (0.534-0.794, p=0.014) | 0.654 (0.516-0.792, p=0.031) |
| Model 9 | CRP ≥21 (mg/dL) and relative bradycardia | 0.714 (0.588-0.840, p=0.001) | 0.726 (0.595-0.856, p=0.002) |
| Model 10 | Na ≤137 (meq/L) and relative bradycardia | 0.790 ( 0.675-0.906, p<0.001) | 0.791 (0.671-0.912, p<0.001) |
| Model 11 | LDH ≥292 (IU/L) and CRP ≥21 (mg/dL) and Na ≤137 (meq/L) | 0.690 (0.562-0.819, p=0.004) | 0.684 (0.548-0.820, p=0.01) |
| Model 12 | LDH ≥292 (IU/L) and CRP ≥21 (mg/dL) and relative bradycardia | 0.674 (0.544-0.804, p=0.009) | 0.684 (0.548-0.820, p=0.01) |
| Model 13 | LDH ≥292 (IU/L) and Na ≤137 (meq/L) and bradycardia | 0.640 (0.508-0.772, p=0.035) | 0.649 (0.510-0.787, p=0.03) |

*All cases consist of *Legionella pneumophila* pneumonia (n=62) and *S. pneumoniae* pneumonia (n=70)

**A-DROP<4 group consist of *Legionella pneumophila* pneumonia (n=42) and *S. pneumoniae* pneumonia (n=40).

LDH: lactate dehydrogenase, CRP: C-reactive protein

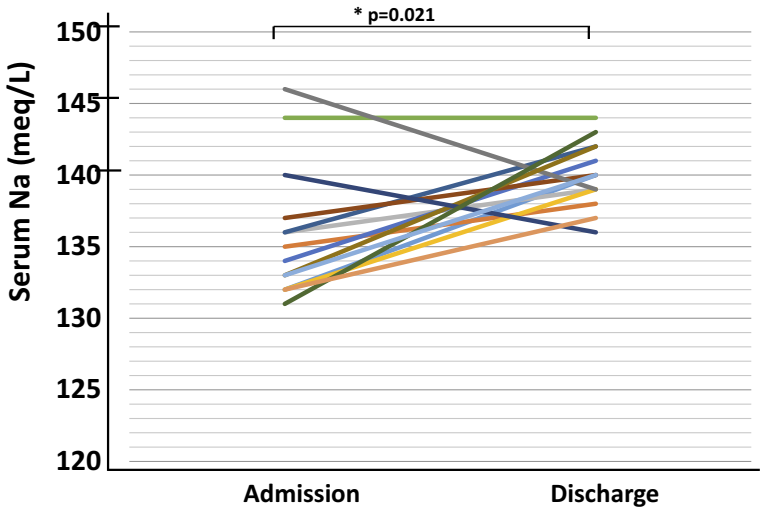


**Figure 5.** **Change in the serum sodium levels during the clinical course.**

**Table 8.** **Comparison of the RICO's Score and New Score.**

| | L-group | S-group | Sensitivity (%) | Specificity (%) | AUC (95%CI, p value) |
|---|---|---|---|---|---|
| RICO's score (≥4) | 16 | 3 | 47.1 | 95.6 | 0.713 (0.597-0.830, p<0.001) |
| RICO's score (≥5) | 6 | 2 | 17.6 | 97.1 | 0.574 (0.451-0.696, p=0.228) |
| New score (≥3) | 21 | 1 | 63.6 | 98.2 | 0.809 (0.703-0.916, p<0.001) |
| New score (≥4) | 9 | 1 | 27.3 | 98.2 | 0.627 (0.561-0.754, p=0.045) |

Total number of patients (L-group, S-group) whose data can be available for RICO's score and/or New score were (n=34, n=68), (n=33, n=56), respectively.

AUC: area under the curve, L-group: *Legionella pneumophila* pneumonia group, S-group: *Streptococcus pneumoniae* pneumonia group, 95%CI: 95% confidence interval

0.045) (Table 6).

### Different clinical model specifications

The four parameters had different HRs for predicting *L. pneumophila* pneumonia. A combination of these parameters also differentiated *L. pneumophila* pneumonia from *S. pneumoniae* pneumonia, with AUCs between 0.653 and 0.828, even in the setting of A-DROP <4, with AUCs ranging from 0.654 to 0.827 (Table 7).

### Change in the serum sodium levels during the clinical course

Of the 14 *L. pneumophila* pneumonia patients for whom data were available, the serum sodium levels at the time of discharge had increased significantly from those at the time of admission (Wilcoxon's signed-rank test: p=0.021) (Fig. 5).

### A comparison of the diagnostic yield for L. pneumophila pneumonia between Rico's score and our new score

To examine the difference in the diagnostic accuracy between Rico's score, which is the most recently developed scoring system for *L. pneumophila* pneumonia, and our new scoring system, we applied the two scores to the data of enrolled patients (Table 8). The total number of patients in the L- and S-groups with available data to determine Rico's score and the new score were n=34 and n=68, and n=33 and n=56, respectively. A Rico's score of ≥4 showed a sensitivity of 47.1% and specificity of 95.6%, with an AUC of 0.713 (95% CI: 0.597-0.830, p<0.001); however, a score of ≥5 was not statistically significant for a diagnosis. In contrast, our new scoring system was reliable for both scores (≥3 and ≥4). In patients with a score of ≥3 in particular, the diagnostic accuracy for *L. pneumophila* pneumonia showed a sensitivity of 63.6% and specificity of 98.2%, with an AUC of 0.809 (95% CI: 0.703-0.916, p<0.001), which was a higher diagnostic yield than that obtained with a Rico's score of 4.

## Discussion

This study demonstrated the application of a novel scoring system for the diagnosis of *L. pneumophila* pneumonia. Furthermore, we found that serum sodium levels tended to be low based on the A-DROP score, which is contrary to the common perception of general physicians. *L. pneumophila* pneumonia and *S. pneumoniae* pneumonia are the most common causes of CAP. The clinical presentation and chest radiographic findings in *L. pneumophila* pneumonia might not be specific in hospitalized patients; however, they pre-

sent with lobar pneumonia, as is also seen in cases of *S. pneumoniae* pneumonia. Differentiation can be difficult, but no report has yet described simple predictive factors for distinguishing *L. pneumophila* pneumonia from *S. pneumoniae* pneumonia.

In this regard, our study also successfully generated a novel scoring system for predicting *L. pneumophila* pneumonia and differentiating it from *S. pneumoniae* pneumonia. *L. pneumophila* pneumonia can be easily diagnosed if the score is ≥3 using 4 simple factors: relative bradycardia, serum LDH levels ≥292 IU/L, CRP levels ≥21 mg/dL, and Na levels ≤137 meq/L. This will enable physicians to treat patients with appropriate empiric antibiotic regimens and facilitate early decision-making. In addition, we indicated the clinical utility of the scoring system in the specifications of the 13 different clinical models. Furthermore, a score of ≥3 with our novel system seemed to be a more reliable and powerful for detecting *L. pneumophila* pneumonia than the previous score known as "Rico's criteria" (≥4) (15, 16). Of note, Rico's criteria were basically developed to rule out *L. pneumophila* pneumonia from cases of CAP due to all respiratory pathogens, whereas the new score in this study was applied to cases of lobar pneumonia suspected of having either *L pneumophila* or *S. pneumoniae*. Regardless of the radiological similarities, the differentiation of *L. pneumophila* pneumonia from *S. pneumoniae* pneumonia will play a pivotal role not only in choosing the proper antibiotic treatment but also in recognizing the possibility of life-threatening situations over a short period of time due to other pathogens.

Interestingly, our study was the first to show that the serum sodium levels were directly associated with the A-DROP score. Patients with less severe *L. pneumophila* pneumonia are likely to have lower values of serum sodium levels than those with severe and/or very severe *L. pneumophila* pneumonia of unknown pathophysiology.

Hyponatremia is common in Legionnaires' disease and is considered to be the result of inappropriate secretion of antidiuretic hormone. However, the precise underlying mechanisms are uncertain, and previous reports have suggested that an alternative explanation is needed (17-19). Recently, Schuetz et al. confirmed that no correlation exists between serum CT- provasopressin (precursor of ADH) and sodium levels in Legionnaires' disease (20); however, their data appeared to show a positive correlation between the serum sodium levels and the disease severity (CURB-65 score). In the present study, the sodium levels returned to the normal range in due course, suggesting a Legionella infection. Thus, hyponatremia might be a valuable marker, especially in less severe cases of pneumonia.

Several limitations associated with the present study warrant mention. First, it was a retrospective study. Second, it had a relatively small number of *L. pneumophila* pneumonia patients. Third, we specifically focused on the differentiation between *L. pneumophila* pneumonia from *S. pneumoniae* pneumonia as representative causes of lobar pneumonia showing similar radiological features and the potential to induce a life-threatening condition.

However, to our knowledge, this study included the largest number of Legionella-infected patients, and our simple predictive scoring system can be used in the setting of lobar pneumonia, which is a characteristic radiological feature of both *S. pneumoniae* pneumonia and *L. pneumophila* pneumonia. Our scoring system warrants further study to ascertain the diagnostic accuracy in all CAP patients with various etiologies.

## Conclusions

This study was the first to show that patients with less severe *L. pneumophila* pneumonia are likely to have lower serum sodium levels than patients with *S. pneumoniae* pneumonia. We also generated a novel scoring system with high specificity using four simple predictive factors.

The current study was approved by the institutional review board of Kyorin University School of Medicine (IRB: H29-013), and written informed consent was waived.

**The authors state that they have no Conflict of Interest (COI).**

### References


1. Suga Y, Urano J, Kangawa T. A retrospective analysis of clinical profiles of eleven Legionella pneumonias: would acute respiratory failure without dyspnea be a good indicator for early diagnosis of Legionella pneumonia? Kokyu To Junkan (Respir Circ) **63**: 689-695, 2015 (in Japanese).
2. Watanabe S. [Two cases of Legionella pneumophila pneumonia with hypophosphatemia]. Rinsho Taieki **42**: 51-54, 2015 (in Japanese).
3. Nishihara Y, Kanemitsu Y, Sado T, Katayama MY, Fukata H, Kita H. A case of secondary thrombotic thrombocytopenic purpura with concomitant Legionella pneumonia during the treatment of rheumatoid arthritis with adalimumab. AJRS: Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respir Soc) **2**: 598-602, 2013 (in Japanese, Abstract in English).
4. Ishii H, Tomioka H, Hirata Y, Sekiya R, Kaneko M, Katsuyama E. Legionella pneumonia presenting as nursing and healthcare-associated pneumonia: an autopsy case report. AJRS: Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respir Soc) **2**: 562-566, 2013 (in Japanese, Abstract in English).
5. Azuma T, Ishida T. A case of nosocomila *Legionella pneumophila* serogroup1 pneumonia. Ann Kurashiki Central Hospital **75**: 275-278, 2012.
6. Kanda A, Yoshida M, Asada N, Nakayama K, Akiho N. [Clinical characterization of 16 cases with Legionalella pneumohpila pneumonia]. J Sendai City Hospital **33**: 3-6, 2013 (in Japanese).
7. Kato H, Murata K, Kashiyama T, Okamoto S, Mikura S, Takamori M. A case of severe Legionella pneumonia in which survival was achieved without sequelae with the use of extracorporeal membrane oxygenation (ECMO). Kansenshogaku Zasshi (J Jpn Assoc Infect Dis) **87**: 375-379, 2013 (in Japanese, Abstract in English).
8. Okuda M, Kashio M, Tanaka J. A case of the usefulness of PCT for monitoring disease activities of sepsis due to Legionella pneumonia. Nihon Kyobu Rinsho (Jpn J Chest Dis) **71**: 71-76, 2012 (in Japanese).

**9.** Hasegawa J, Hirokawa T, Endo K. A case of Legionnaires' infection with meningeal irritation and abnormal cerebrospinal fluid. Clin Neurol **53**: 526-530, 2013.

**10.** Nomura N, Ito T. The clinical usefulness of serum procalcitonin measurement for assessing the disease course in severe Legionella pneumonia associated with rhabdomyolysis and multiple organ dysfunction. Nihon Kyobu Rinsho (Jpn J Chest Dis) **74**: 792-798, 2015 (in Japanese).

**11.** Torikai K, Nemoto T, Hirose M, et al. A case of Legionella pneumonia with cerebellar dysfunction complicated by disseminated intravascular coagulation. J St. Marianna Univ **40**: 259-263, 2013.

**12.** Suehiro T, Ichiki Y, Koike M. [A case of successfully treated Legionella pneumophila pneummonia with rapid diagnosis at three days after the initial onset]. Rinsho To Kenkyu **90**: 111-113, 2013 (in Japanese).

**13.** Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. Clin Microbiol Infect **6**: 633-634, 2000.

**14.** Miyashita N, Matsushima T, Oka M; Japanese Respiratory S. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med **45**: 419-428, 2006.

**15.** Fiumefreddo R, Zaborsky R, Haeuptle J, et al. Clinical predictors for Legionella in patients presenting with community-acquired pneumonia to the emergency department. BMC Pulm Med **9**: 4, 2009.

**16.** Haubitz S, Hitz F, Graedel L, et al. Ruling out Legionella in community-acquired pneumonia. Am J Med **127**: 1010.e11-1010.e19, 2014.

**17.** Richards V. Hyponatremia in legionnaires' disease. Ann Intern Med **90**: 132-133, 1979.

**18.** Ellis M, Dunbar E, Watson B. Hyponatraemia in legionnaires' disease. Br Med J (Clin Res Ed) **284**: 1047, 1982.

**19.** Miller AC. Hyponatraemia in Legionnaires' disease. Br Med J (Clin Res Ed) **284**: 558-559, 1982.

**20.** Schuetz P, Haubitz S, Christ-Crain M, et al. Hyponatremia and anti-diuretic hormone in Legionnaires' disease. BMC Infect Dis **13**: 585, 2013.