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Committee Report

Validation of a diagnostic score model for the prediction of *Legionella pneumophila* pneumonia☆

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ABSTRACT

Background: Community-acquired pneumonia (CAP) due to *Legionella* has a high mortality rate in patients who do not receive adequate antibiotic therapy. In a previous study, we developed a simple Legionella Score to distinguish patients with *Legionella* and non-*Legionella* pneumonia based on clinical information at diagnosis. In the present study, we validated this Legionella Score for the presumptive diagnosis of *Legionella* CAP.

Methods: This validation cohort included 109 patients with *Legionella* CAP and 683 patients with non-*Legionella* CAP. The Legionella Score includes six parameters by assigning one point for each of the following items: being male, absence of cough, dyspnea, C-reactive protein (CRP) $\geq$ 18 mg/dL, lactate dehydrogenase (LDH) $\geq$ 260 U/L, and sodium < 134 mmol/L.

Results: When the *Legionella* CAP and non-*Legionella* CAP were compared by univariate analysis, most of the evaluated symptoms and laboratory test results differed substantially. The six parameters that were used for the Legionella Score also indicated clear differences between the *Legionella* and non-*Legionella* CAP. All *Legionella* patients had a score of 2 points or higher. The median Legionella Scores were 4 in the *Legionella* CAP cases and 2 in the non-*Legionella* CAP cases. A receiver operating characteristics curve showed that the area under the curve was 0.93. The proposed best cutoff, total score $\geq$3, had sensitivity of 93% and specificity of 75%.

Conclusion: Our Legionella Score was shown to have good diagnostic ability with a positive likelihood of 3.7 and a negative likelihood of 0.10.

Abbreviations: AUC, area under the ROC curve; CAP, community-acquired pneumonia; CRP, C-reactive proteins; IQR, interquartile ranges; LAMP, loop-mediated isothermal amplification method; LDH, lactate dehydrogenase; MIC, minimum inhibitory concentration; NLH, negative likelihood; NPV, negative predictive value; PCR, polymerase chain reaction; PLH, positive likelihood; PPV, positive predictive value; ROC, receiver operating characteristics.

☆ All authors meet the ICMJE authorship criteria.

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1. Background

Legionella species are an important cause of community-acquired pneumonia (CAP), which is a potentially fatal pneumonia that develops rapidly [1–3]. Therapeutic failure and unsuccessful treatment of *Legionella* infection has also been documented, but delays in medical attention or untimely or inappropriate antimicrobial treatment is probably the main cause [4,5]. Thus, early identification of *Legionella* infection is important because it affects the timing and choice of empiric antibiotic therapy and reduces the risk of adverse outcomes. Among *Legionella* species, *Legionella pneumophila* is considered to be responsible for up to 80–90% of human infections and is the most important etiologic agent of Legionnaires' disease [6–9].

The number of reported *Legionella* pneumonia cases is increasing gradually in Japan and accounts for over 2100 cases per year (154 cases in 2000 and 751 cases in 2010), and outbreaks have occurred in hot spring conditions every year. Although the early administration of appropriate antibiotic therapy is the most important factor for successful treatment, most cases were diagnosed using a urinary antigen test, which appears to have excellent specificity but only modest sensitivity [10]. In addition, high-quality studies showed lower sensitivity for this test [10]. Thus, many researchers have proposed rapid or simple scoring systems based on clinical and laboratory findings for the presumptive diagnosis of *Legionella* pneumonia, but the sensitivities and specificities of these scoring systems have not been sufficient [11–16]. Recently, we developed the Legionella Score to distinguish patients with *Legionella* and non-*Legionella* pneumonia based on clinical information at diagnosis using patients with *Legionella* CAP, *Streptococcus pneumoniae* CAP, and *Mycoplasma pneumoniae* CAP [17].

The purpose of the present study was to identify a means of rapidly distinguishing *Legionella* CAP from other causes of CAP in daily clinical practice. We validated the Legionella Score including both *Legionella* and non-*Legionella* CAP utilizing a standard method [18].

2. Methods

2.1. Study population

This study was conducted the 25 institutions between April 2010 and March 2018 and was an independent of a previous development cohort [17]. A complete list of participating facilities is provided in the appendix. We enrolled adolescent (16–19 years-old) and adult patients (≤65 years-old) who were diagnosed with CAP. Exclusion criteria included immunosuppressive illness (*i.e.*, HIV positive, neutropenia secondary to chemotherapy, use of >20 mg/day prednisone or other immunosuppressive agents, and history of organ transplant); hospitalization in the preceding 30 days; residence in a nursing home or extended care facility; and active tuberculosis. Patients with *L. pneumophila* pneumonia mixed with other microorganisms were excluded from this study. The study protocol was approved by the Ethics Committee at Kawasaki Medical School and all participating facilities.

We used a standardized questionnaire for collecting clinical information. Information on patient background, clinical signs, symptoms, laboratory data, and clinical course after admission to hospital were collected. Pneumonia risk assessment was evaluated using predictive rules using a 5-point scoring systems, the CURB-65 score [19] and the A-DROP score [20]. The A-DROP score (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure) is a modified version of the CURB-65 score based on Japanese situations [20].

2.2. Microbiological laboratory tests

Legionella was considered to be the definitive causative agent with a positive urinary antigen test, culture, polymerase chain reaction (PCR) or loop-mediated isothermal amplification method (LAMP), and a four-fold rise in antibody titer level between paired sera. Microbiological tests for the detection of other pathogens, cultures, antigen detection test, real-time PCR, LAMP and serological tests were performed as described previously [21].

2.3. Statistical analysis

Fisher's exact test for binary variables and Mann–Whitney *U* test for a continuous variables were used to compare two groups. The Legionella Score included parameters that had a strong relationship with *Legionella* diagnosis when analyzed by logistic regression analysis ($P < 0.001$). One point was assigned for each parameter. The cutoff value of a continuous parameter was defined by the value that gave the best Youden's Index. A receiver operating characteristics (ROC) curve and area under the ROC curve (AUC) were assessed as appropriate.

Positive likelihood (PLH) and negative likelihood (NLH) were calculated as follows: PLH = sensitivity/(1-specificity) and NLH = (1-sensitivity)/specificity. When PLH and NLH are away from a null value of 1, the test largely changed the probability of the disease.

Positive predictive value (PPV) and negative predictive value (NPV) were estimated from the diagnostic accuracy. For this predictive value analysis, the prevalence of *Legionella* among patients with CAP was assumed as 2–16% [22–28]. Data analysis was performed using Excel Toukei 2015 (SSRI, Tokyo, Japan).

2.4. Legionella Score

To identify diagnostic predictors of *Legionella* CAP, we used baseline parameters of 176 patients with *Legionella* CAP and 419 patients with non-*Legionella* CAP as reported previously [17]. Logistic regression analysis revealed that being male, absence of cough, having dyspnea, elevated C-reactive proteins (CRP) level, high lactate dehydrogenase (LDH) level, and low sodium (Na) level increased the probability of *Legionella* pneumonia within our *P* value criteria ($P < 0.001$) (Table 1). Absolute standardized partial regression coefficient values of these six parameters ranged from 0.54 to 0.94. AUC values were 0.84, 0.77, and 0.68 for CRP, LDH, and Na, respectively (Fig. 1). Judged from Youden's index, the best cutoffs were CRP ≥17.5 mg/dL, LDH ≥259 U/L, and Na < 134 mmol/L (Fig. 1). The cutoffs for CRP and LDH were rounded as CRP ≥18 mg/dL and LDH ≥260 U/L for the actual scoring system. Eventually, the Legionella Score was defined by assigning one point for each of the following items: being male, absence of cough, dyspnea, CRP ≥18 mg/dL, LDH ≥260 U/L, and Na < 134 mmol/L.

The median Legionella Score was 4 (interquartile ranges [IQR] 3–5) in the *Legionella* CAP group, 2 (IQR 1–3) in the *S. pneumoniae* CAP group, and 1 (IQR 0–2) in the *M. pneumoniae* CAP group. A total score ≥3 showed the best Youden index of 0.69, which was calculated from sensitivity of 88% and specificity of 81%. When a total score ≥4 was set up the cut-off level, the Youden index was 0.61, which was calculated from sensitivity of 66% and specificity of 95%.

3. Results

3.1. Patient characteristics

During the study period, 109 patients with *L. pneumophila* CAP were recorded. For comparison we used 683 patients with non-*Legionella* CAP who were diagnosed during the study period.

Table 1
Logistic regression analysis for *Legionella* diagnosis in the development cohort.

	Odds ratio (95% CI)	*P* value	sprc
Age (10 year)	1.02 (1.00–1.04)	0.075	0.37
Male	3.79 (1.84–7.77)	<0.001	0.64
Current smoker	3.04 (1.56–5.93)	0.001	0.49
Ex-smoker	1.32 (0.63–2.77)	0.467	0.11
Body temperature (Celsius)	1.34 (0.91–1.98)	0.134	0.24
Cough	0.21 (0.09–0.47)	<0.001	−0.54
Sputum	0.62 (0.33–1.18)	0.145	−0.23
Dyspnea	6.41 (3.52–11.67)	<0.001	0.90
Chest pain	0.72 (0.26–1.96)	0.518	−0.10
Psychosis	1.30 (0.64–2.64)	0.473	0.10
Headache	0.96 (0.41–2.24)	0.926	−0.01
Gastrointestinal symptom	1.03 (0.38–2.79)	0.950	0.01
White blood cell (1000/μL)	1.03 (0.98–1.08)	0.291	0.15
Platelets (10,000/μL)	1.00 (0.96–1.04)	0.878	−0.02
C-reactive protein (mg/dL)	1.08 (1.05–1.12)	<0.001	0.93
Aspartate transaminase (10 U/L)	0.98 (0.93–1.02)	0.313	−0.22
Lactate dehydrogenase (10 U/L)	1.05 (1.02–1.08)	<0.001	0.94
Creatinine (mg/dL)	0.81 (0.56–1.18)	0.280	−0.14
Sodium (mmol/L)	0.85 (0.80–0.91)	<0.001	−0.69
Creatine kinase (100 U/L)	1.03 (1.00–1.07)	0.069	0.46

sprc: standardized partial regression coefficient.

Table 2 shows the clinical characteristics of *Legionella* patients and non-*Legionella* patients on admission to hospital. Among 109 patients with *L. pneumophila* CAP (88 cases were serogroup 1), 80 patients were urinary antigen test positive, 37 patients were culture positive, 36 patients were PCR and/or LAMP positive, and 24 patients demonstrated a four-fold antibody seroconversion.

Among the 683 patients with non- *Legionella* CAP, a microbiological diagnosis was established in 205 patients (30%). The most common pathogens were *S. pneumoniae* (71 patients) followed by *Haemophilus influenzae* (45 patients), *M. pneumoniae* (43 patients), *Moraxella catarrhalis* (19 patients), *Staphylococcus aureus* (14 patients), *Klebsiella pneumoniae* (10 patients), and anaerobes (10 patients).

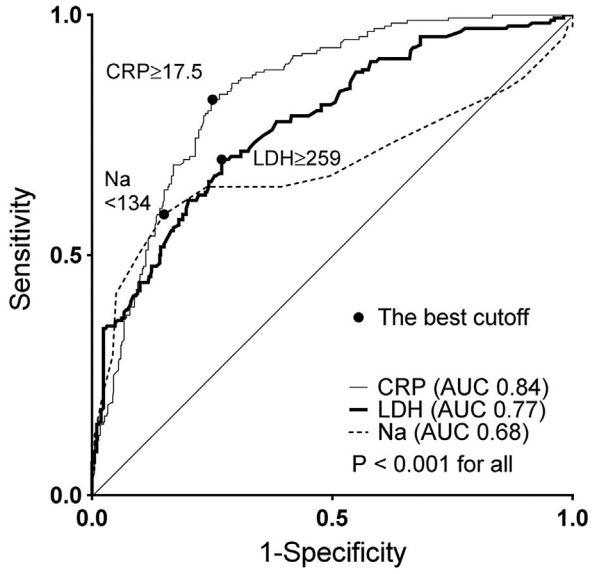

Fig. 1. Receiver operating characteristics curve. Cut-off of C-reactive protein (CRP), lactate dehydrogenase (LDH), and sodium (Na) in the development cohort. AUC: area under the receiver operating characteristics curve.

When the *Legionella* CAP and non-*Legionella* CAP cases were compared by univariate analysis, most of the evaluated symptoms and laboratory test results differed substantially. Patients in with *Legionella* CAP were more frequently male and current smokers. Although dyspnea and psychosis were more commonly observed in the *Legionella* CAP group, cough and sputum production were more frequent in the non-*Legionella* CAP group. Inflammatory markers such as body temperature, white blood cell count, and CRP were markedly elevated in the *Legionella* population. The *Legionella* CAP cases also featured higher levels of cell injury-related enzymes, including aspartate transaminase, LDH and creatine kinase. Na level was significantly lower in patients with *Legionella* CAP. The median periods from occurrence to the first visit to hospital were 4.5 days (IQR 2–6) in the *Legionella* CAP group and 4.5 days (IQR 2–7) in the non-*Legionella* CAP group.

Pneumonia severity was identical in both groups, with a median score of 2 using CURB-65 (IQR 1–3) and 2 using A-DROP (IQR 1–2) in the *Legionella* CAP group, and 2 using CURB-65 (IQR 1–2) and 2 using A-DROP (IQR 1–2) in the non-*Legionella* CAP group.

3.2. Validation of the Legionella Score

The six parameters that were used for the Legionella Score indicated clear differences between the *Legionella* and non-*Legionella* CAP groups in this validation step (Table 2). All *Legionella* patients had a score of 2 points or higher. The median Legionella Score was 4 (IQR 4–5) in the *Legionella* CAP group and 2 (IQR 1–3) in the non-*Legionella* CAP group (Table 2).

The ROC curve showed that the AUC was 0.93 ($P < 0.001$, Fig. 2). The proposed best cutoff, total score ≥3, had a sensitivity of 93% and specificity of 75%. Thus, PLH and NLH were 3.7 and 0.10, respectively.

Relationship between pneumonia severity and Legionella Score in 109 patients with *L. pneumophila* CAP were presented in Table 3. High points using the A-DROP system demonstrated the high Legionella Score for prediction of the *Legionella* pneumonia. The proposed best cutoff, total score ≥3, had a sensitivity of 64% in A-DROP 0 point, 93% in A-DROP 1 point and 98% in A-DROP 2 points.

Based on the assumption that *Legionella* spp. account for 2–16% of CAP cases [22–28], PPV and NPV were calculated as shown in Table 3. For example, if the pretest probability was 4%, PPV and NPV were 13.2% and 99.6%. This means that a patient with a Legionella Score of 0–2 or 3–6 has 0.4% or 13.2% risk of the *Legionella* pneumonia, respectively (Table 4).

4. Discussion

In the former development cohort, we included only selected CAP patients as controls who had established causative pathogens: *S. pneumoniae* and *M. pneumoniae* [17]. *S. pneumoniae* is the leading cause of CAP and *M. pneumoniae* is the leading cause of atypical pneumonia and second or third leading cause of CAP. In this validation cohort, we included all CAP patients as controls, although the causative pathogens in 70% cases were unknown. Although these two cohorts analyzed different types of non-*Legionella* CAP as the controls, the results of the clinical and laboratory differences between *Legionella* CAP and non-*Legionella* CAP cases were identical in both the development and validation cohorts. In addition, the six parameters that were used for the Legionella Score in the development cohort indicated clear differences between the *Legionella* and non-*Legionella* cohorts in the validation step.

Table 2
Patient characteristics.

	All	*Legionella*	Non-*Legionella*	*P* value
Number	792	109	683	
Age (year)	67 (46–78)	66 (54–69)	69 (40.5–80)	0.034
Male	500 (63.1%)	99 (90.8%)	401 (58.7%)	<0.001
Current smoker	178 (22.5%)	58 (53.2%)	120 (17.6%)	<0.001
Co-morbid conditions				
Diabetes mellitus	143 (18.1%)	23 (20.2%)	120 (17.7%)	0.4206
Chronic lung disease	276 (34.3%)	21 (19.3%)	255 (37.3%)	0.0002
Chronic heart disease	91 (11.5%)	9 (8.3%)	82 (12.0%)	0.3312
Cerebrovascular disease	76 (10.0%)	8 (7.3%)	68 (10.0%)	0.4846
Chronic liver disease	43 (5.4%)	5 (4.6%)	38 (5.6%)	0.8221
Chronic renal disease	42 (5.3%)	5 (4.6%)	37 (5.4%)	>0.9999
Neoplastic disease	43 (5.4%)	2 (1.8%)	41 (6.0%)	0.1067
Clinical symptoms and sign				
Cough	605 (76.4%)	39 (35.8%)	566 (82.9%)	<0.001
Sputum	533 (67.3%)	60 (55.0%)	473 (69.3%)	0.004
Dyspnea	255 (32.2%)	62 (56.9%)	193 (28.3%)	<0.001
Chest pain	81 (10.2%)	8 (7.3%)	73 (10.7%)	0.393
Psychosis	124 (15.7%)	44 (40.4%)	80 (11.7%)	<0.001
Headache	103 (13.0%)	12 (11.0%)	91 (13.3%)	0.645
Gastrointestinal symptom	93 (11.7%)	17 (15.6%)	76 (11.1%)	0.199
Body temperature (Celsius)	38.6 (38.0–39.2)	39.4 (38.8–40.0)	38.5 (38.0–39.0)	<0.001
Laboratory findings				
White blood cell (1000/μL)	10.1 (7.3–13.3)	11.4 (9.0–14.8)	9.9 (7.1–12.9)	<0.001
Platelets (1000/μL)	193 (153–253)	167 (128–213)	202 (156–258)	<0.001
C-reactive protein (mg/dL)	13.2 (6.2–21.9)	27.8 (23.1–34.8)	11.4 (5.4–17.6)	<0.001
Aspartate transaminase (U/L)	27 (19–46)	68 (40–133)	25 (18–37)	<0.001
Lactate dehydrogenase (U/L)	235 (197–310)	337 (257–457)	226 (188–281)	<0.001
Creatinine (mg/dL)	0.83 (0.64–1.06)	1.08 (0.90–1.69)	0.79 (0.62–1.00)	<0.001
Sodium (mmol/L)	137 (135–140)	133 (130–137)	138 (136–140)	<0.001
A-DROP Score				
0	51	14	37	0.0097
1	212	28	184	0.8170
2	341	42	299	0.3487
3	153	22	131	0.7946
4	33	3	30	0.6065
5	2	0	2	>0.999
Pathogen				
Legionella pneumophila	109	109	0	
Streptococcus pneumoniae	71	0	71	
Haemophilus influenza	45	0	45	
Mycoplasma pneumoniae	43	0	43	
Moraxella catarrhalis	19	0	19	
Staphylococcus aureus	14	0	14	
Klebsiella pneumoniae	10	0	10	
Anaerobes	10	0	10	
Unknown	471	0	471	
Legionella Score	2 (1–3)	4 (4–5)	2 (1–3)	<0.001
0	54	0	54	
1	159	0	159	
2	210	4	206	
3	162	8	154	
4	109	29	80	
5	81	52	29	
6	17	16	1	

Median with inter-quartile range is presented for continuous variables.
Number of patients with percentage is presented for binary variables.
P value is for comparison between 109 *Legionella* patients and 683 non-*Legionella* patients. Fisher's exact test for binary variables and Mann–Whitney *U* test for continuous variables are used.

In the present study, we evaluated other clinical prediction scores for presumptive diagnosis of *Legionella* pneumonia [12,13,15]. The sensitivity and specificity of the Winthrop-University Hospital point scoring scale [12], in which the category of "highly probable" is defined as "positive for the diagnosis of Legionellosis", were 72% and 70%, respectively. In the Community-Based Pneumonia Incidence Study Group score [13], in which the category of "high probability" was defined as "positive for the diagnosis of Legionellosis", sensitivity was 41% and specificity was 87%. In the Fiumefreddo score [15], in which the cut-off level of ≥4 points was defined as "positive for the diagnosis of Legionellosis", sensitivity was 46% and specificity was 92%. Our Legionella Score demonstrated sensitivity of 93%, specificity of 75%, PLH of 3.7, and NLH of 0.10. These values meant a total score <3 points decreased the probability of *Legionella* pneumonia to one-tenth, and that a total score of ≥3 increased the probability of *Legionella* pneumonia by 3.7-fold.

Being male, dyspnea, and absence of cough were identified as independent predictors of *Legionella* CAP in both the development and validation cohorts [17]. Previous Japanese studies also demonstrated that *Legionella* CAP was more frequently seen in male patients [29,30]. The same results were also observed in the

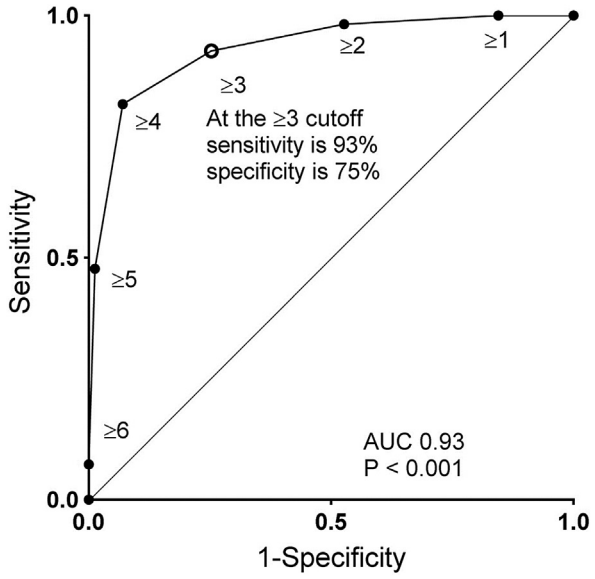

Fig. 2. Receiver operating characteristics curve. Diagnostic ability of the Legionella Score in the validation cohort. AUC: area under the receiver operating characteristics curve.

Legionella surveillance system of Japan conducted by the National Institute of Infectious Diseases [31]. However, these parameters were not identified as independent predictors of *Legionella* CAP in other countries [12,13,15,16]. There is no clear reason why the diagnostic predictors of *Legionella* CAP are different between Japan and other countries. Hot springs or 24-h circulation type baths are widely utilized as part of Japanese culture, and outbreaks of Legionnaires' disease have occurred every year at hot spring or bathing facilities. Cultural differences may reflect the differences in independent predictors of *Legionella* CAP between Japan and other countries.

The pretest probability is required to estimate PPV and NPV along with sensitivity and specificity. *Legionella* spp. are a low prevalence causative pathogen of pneumonia compared with other microorganisms, including *S. pneumoniae, H. influenzae*, and *M. pneumoniae*. The prevalence of *Legionella*, which can be easily affected by the area of surveillance, study year, and inclusion criteria, has been reported as 2–16% [22–28]. Our scoring system, with a cutoff score of ≥3, had good NLH (Fig. 2). When the post-test probability is sufficiently low, routine assessment using a *Legionella* urine antigen test is not recommended for such patients. Even though a high score with the Legionella Score cannot rule-in *Legionella* pneumonia, given the fierce nature of *Legionella* pneumonia, *Legionella* coverage by quinolone or macrolide therapy may be considered when the post-test probability is considered as high.

Table 3
Relationship between pneumonia severity using A-DROP system and Legionella Score in 109 patients with *L. pneumophila* CAP.

A-DROP system	Legionella Score						
	0 point	1 point	2 points	3 points	4 points	5 points	6 points
0 point		1	4	3	4	2	
1 point		1	1	6	10	9	1
2 points			1	3	11	24	3
3 points			1	1	7	8	5
4 points						3	

Data are presented number of patients.

Table 4
Positive and negative predictive values (PPV, NPV) of the Legionella Score with a cutoff ≥ 3.

Pretest probability	PPV	NPV	1-NPV
2%	7.0%	99.8%	0.2%
4%	13.2%	99.6%	0.4%
8%	24.2%	99.2%	0.8%
16%	41.1%	98.2%	1.8%

Our study had several limitations. First, the present study was evaluated in a case–control manner. Thus, overestimation of the diagnostic ability of the Legionella Score might be possible due to selection bias. Second, the score was evaluated in Japan only. Therefore, applicability to non-Japanese CAP patients is not clear. Third, PPV and NPV estimation required the pretest probability of *Legionella*. If *Legionella* pneumonia was more or less prevalent in a region, the PPV and NPV in that region will be greatly different.

5. Conclusion

We developed the Legionella Score to distinguish patients with *Legionella* and non-*Legionella* pneumonia based on the clinical information at diagnosis. The Legionella Score was based on being male, absence of cough, dyspnea, elevated CRP and LDH levels, and low Na level. The scoring system was shown to have good diagnostic ability exception of mild severity pneumonia with A-DROP 0 point. The cutoff, a Legionella Score ≥3, provided sensitivity of 93%, specificity of 75%, PLH of 3.7, and NLH of 0.10.

Ethical approval and consent to participate

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

Funding

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Availability of data and materials

The data will not be shared with 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, NH and NO drafted the manuscript, and all authors contributed substantially to its revision. All the authors read and approved the final manuscript.

Consent for publication

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

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consisted of: Asahigaoka Hospital, Heisei Hospital, Kaneda Hospital, Kasaoka Daiichi Hospital, Kawasaki Medical School Hospital, Kawasaki Hospital, Kawasaki Medical School General Medical Center, Kenritsu Hiroshima Hospital, Kimura Clinic, Kojima Central Hospital, Kurashiki Daiichi Hospital, Kurashiki Memorial Hospital, Mie National Hospital, Nagasaki Genbaku Hospital, Nakahama Clinic, Nakatani Geka Hospital, Nakashima Hospital, Okayama Kyoritsu General Hospital, Okayama Saidaiji Hospital, Saijo Aijukai Hospital, Satou Memorial Hospital, Takahashi Central Hospital, Tamano Central Hospital, Tamashima Central Hospital, and University of Miyazaki Hospital.

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