INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Discrimination between Legionnaires' Disease and Pneumococcal Pneumonia Based on the Clinical and Laboratory Features: A Quantitative Approach Using the Modified Winthrop-University Hospital Weighted Point System

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Abstract

Objective Legionnaires' disease (LD) is a common form of lobar pneumonia, but the optimum diagnostic modality has long been a subject of debate due to incomplete sensitivity and specificity. A delay in the initiation of specific therapy for LD is associated with increased mortality. The decision to treat a patient for *Legionella* must be made quickly. The purpose of this study was to evaluate the ability of the modified Winthrop-University Hospital WUH system to identify LD while discriminating against pneumococcal pneumonia at the time of hospitalization for community-acquired pneumonia.

Methods Five patients with LD and 13 patients with pneumococcal pneumonia were retrospectively analyzed.

Results The WUH system identified 4 of 5 patients with LD (sensitivity, 80%) while excluding legionellosis in 12 of 13 patients with pneumococcal pneumonia (specificity, 92%). The positive and negative likelihood ratios were 10.4 and 0.2. The area under the receiver operating characteristic curve was 0.969.

Conclusion The WUH system is useful for obtaining a rapid presumptive clinical diagnosis of LD. Further investigation with a larger number of patients is strongly recommended.

Key words: Legionnaires' disease, WUH system, pneumococcal pneumonia

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Introduction

Legionnaires' disease (LD) is a life-threatening community acquired infection (1). Failure to diagnose LD is presumed to be partly due to a lack of clinical awareness among primary care physicians and the challenging nature of its diagnosis (2, 3). Many physicians treat community-acquired pneumonia (CAP) mainly with β-lactam antibiotics, which are ineffective against intracellular pathogen such as *Legionella* sp. (4) Because a delay in the initiation of therapy targeting LD increases mortality (5), the decision to treat a patient for *Legionella* must be made quickly.

The most widely used rapid diagnostic procedure, a urine *Legionella* antigen test, only identifies *Legionella pneumophila* serogroup 1 and may not yield positive test results for several days after the onset of symptoms (6) or in Legionnaires' patients with cellular immune dysfunction in whom the bacterial burden is large enough to develop disease but too small to be detected by a urine antigen test (7). Therefore, developing an objective diagnostic algorithm solely based on the clinical features and primary laboratory tests would assist physicians in initiating specific antimicrobial therapy for LD in a timely manner. In addition, antimicrobial decision-making would be greatly facilitated if the algorithm could discern between severe pneumococcal pneumo-

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Table 1. Winthrop-University Hospital Weighted Point Modified System.

	Qualifying conditions	point score
Clinical features		
Temperature > 39˚C	With relative bradycardia	+5
Headache	Acute onset	+2
Mental confusion/lethargy	Not drug induced	+4
Ear pain	Acute onset	-3
Non-exudative pharyngitis	Acute onset	-3
Hoarseness	Acute not chronic	-3
Sputum (purulent)	Excluding AECB	-3
Hemoptysis	Mild/moderate	-3
Chest pain (pleuritic)	Acute onset	-3
Loose stools/watery diarrhea	Not drug induced	+3
Abdominal pain	With/without diarrhea	+1
Renal failure	Acute (not chronic)	+3
Shock/hypotension	Excluding cardiac/pulmonary causes	-5
Splenomegaly	Excluding non-CAP causes	-5
Lack of response to β-lactam antibiotics	After 72 h (excluding viral pneumonias)	+5
Laboratory features		
Chest X-ray	Rapidly progressive asymmetric infiltrates	+3
Severe hypoxemia with A-a gradient > 35	Acute onset	-5
Hyponatremia	Acute onset	+1
Hypophosphatemia	Acute onset	+5
AST/ALT > normal range	Acute onset	+2
Total bilirubin > normal range	Acute onset	+1
LDH > 400 U/L	Acute onset	-5
CPK > normal range	Acute onset	+4
CRP > 30mg/dL	Acute onset	+5
Cold agglutinin titer ≥ 1:64	Acute onset	-5
Severe relative lymphopenia (<10%)	Acute onset	+5
Ferritin > 2 × normal range	Acute onset	+5
Microscopic hematuria	Excluding trauma, BPH, Foley catheter, bladder/renal neoplasms	+2
	Likelihood of Legionella	
Total point score	> 15 Legionella very likely	
	5 - 15 Legionella likely	
	< 5 Legionella unlikely	

AECB: acute exacerbation of chronic bronchitis, BPH: benign prostatic hyperplasia, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, CRP: C-reactive protein

nia and *Legionella* pneumonia.

The modified Winthrop-University Hospital's weighted point system (WUH system) for the diagnosis of LD was developed by Cunha et al. in 2008 (8, 9) to enable physicians to tentatively diagnose this disease on the day of a patient's encounter. In the present study, patients with CAP caused either by *Streptococcus pneumoniae* or *Legionella* species were retrospectively analyzed, and the validity of the WUH system in discriminating the two diseases was investigated.

Materials and Methods

Study design and inclusion of patients

Patients hospitalized at Saga University Hospital from January 2004 to December 2013 were screened for inclusion in this study by examining the laboratory records for positive results of sputum *Legionella* loop-mediated isothermal amplification (LAMP) tests and for blood culture or sputum culture positive for *Streptococcus pneumoniae*. All of the patients included in the study had initial clinical presentations and chest radiograph findings that were consistent with CAP.

Patients with positive results of sputum *Legionella* LAMP tests were included in the *Legionella* case group (LG). The pneumococcal pneumonia group (PG) consisted of patients with blood or sputum cultures that were positive for *S. pneumoniae* but negative for the sputum *Legionella* LAMP tests. Patients were excluded from the study if there was any evidence of coinfection for any other pathogen. In the PG group, patients were excluded if their severity was mild to moderate based on the A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure) system, which was proposed as a semiquantitative stratification of CAP severity by the Japanese Respiratory Society (JRS) (10). Conversely, we investigated all patients in the LG, because this system might underestimate the severity of cases with LD (11).

Data collection

Patients' data obtained on admission were retrospectively reviewed by medical records. The items utilized for the WUH system are shown in Table 1. A total score of >15 has been reported to make an LD diagnosis highly probable by the original investigators (9). If the data were not evaluated

Table 2. **Patient Characteristics.**

	Legionella n=5	Pneumococcus n=13	p value
Age (median)	63	71	0.043
Gender (male)	4	11	1
Smoking	4	7	0.5956
Underlying comorbidities			
Chronic heart disease	0	1	1
Chronic lung disease	0	4	0.2778
Chronic renal failure	1	2	1
Use of immunosuppressant	2	4	1
Diabetes mellitus	2	5	1
Malignancy	3	2	0.0987
Positive Gram stain	0	12	0.0007
Positive urinary Legionella antigen	3		
Clinical outcome			
Ventilator support	3	6	1
death	1	3	1

or recorded, they were assumed to be normal, hence no score was assigned. Relative bradycardia was defined as an increase in the heart rate of less than 10 beats/min/1-℃ increase in temperature, with the pulse rate ranging from 38.9 to 41.1℃ (8). In addition to the clinical and laboratory data required for the WUH system, the following data were also investigated: gender, age, smoking status, underlying comorbidities, symptoms, sputum Gram stain, presence or absence of pleural fluid, *Legionella* urinary antigen test, requirement for ventilator, and in-hospital mortality.

Statistical analysis

The significance of differences between the LG and PG were determined using the SPSS Statistics version 20 software program (IBM, Japan). A p value of <0.05 was considered to be statistically significant. Sensitivities, specificities, and positive and negative likelihood ratios were derived from the WUH system, defining scores of >15 as positive and scores of ≤15 as negative. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were measured as an index of discrimination between the two groups.

Results

Five patients had LD without any evidence of coinfection. Nineteen patients had pneumococcal pneumonia with no evidence of LD or coinfection. In the LG, two patients were considered severe and three patients moderate based on the A-DROP system. Among the 19 patients with pneumococcal pneumonia, 6 were excluded because their disease severity was mild to moderate based on the A-DROP system (4 patients' severity was mild and 2 patients' was moderate). Thus, 13 patients comprised the PG.

Patient characteristics

The patient characteristics are shown in Table 2. The patients in the LG tended to be younger than those in the PG (63 vs. 71 years, p=0.043). The diagnostic yield of Gram stain was significantly higher in the PG patients (p=0.0007). In the PG, 12 patients' sputum gram stains revealed Gram-positive diplococci. Two patients in the LG were negative for the urinary *Legionella* antigen. No marked difference was noted in terms of gender distribution, smoking status, underlying comorbidities, using of immunosuppressant, need for ventilator assistance, or mortality between the groups.

Parameters of the WUH system

The parameters of the WUH system are shown in Table 3. Temperature >39℃ with relative bradycardia was seen only in the LG (p=0.0001). Headache was more common in the LG than in the PG (p=0.0441). No differences in other symptoms were statistically significant. There was no significant difference between the LG and PG in terms of hypophosphatemia (1 of 4 patients vs. 0 of 3 patients), increased ferritin (3 of 4 patients vs. 2 of 3 patients), microscopic hematuria (3 of 4 patients vs. 2 of 8 patients). Titers for cold agglutinins were not drawn on any patient. No differences in other laboratory criteria were statistically significant.

Figure shows the scores of the WUH system for the LG and the PG. For the LG, the median score on admission was 23, which was significantly higher than the corresponding score of 6 for the PG (p=0.002). One patient's score in the PG was remarkably high (score 22), because of the presence of high point parameters, such as mental confusion, increased creatine phosphokinase (CPK), increased ferritin, and increased C-reactive protein (CRP). This patient had negative findings for the sputum *Legionella* LAMP tests. One patient's score in the LG was exceptionally low, because the patient's disease severity on admission was mild enough to reveal only a few parameters, such as headache, renal failure, and microscopic hematuria. Four patients in the LG (80%) scored "very likely" in contrast to the PG, in which only 1 patient (8%) scored that degree of likelihood (p=0.0077).

Thus, the sensitivity for the WUH system for LD was 80% and the specificity 92%, resulting in positive and negative likelihood ratios of 10.4 and 0.2, respectively. The ROC analysis indicated that the AUC of the WUH system was 0.969 [95% confidence interval (CI), 0.895 to 1.0].

Discussion

The present study confirmed that the WUH system is very effective in both ruling in and ruling out LD. Given that the timely identification of LD still remains challenging even for seasoned clinicians, this clinical algorithm is a useful alternative to the conventional diagnostic procedure not only because it demonstrates diagnostic accuracy for LD but also because it enables clinicians to distinguish between LD and non-LD on the basis of primary or secondary laboratory data alone.

Legionella species and *S. pneumoniae* are frequent causes of severe CAP (12). The JRS guideline recommends combi-

Table 3. Parameters of Winthrop-University Hospital Weighted Point Modified System.

	Qualifying conditions	point score	Legionella n=5	Pneumococcus n=13	p value
Clinical features					
Temperature > 39˚C	With relative bradycardia	+5	5	0	0.0001
Headache	Acute onset	+2	3	1	0.0441
Mental confusion/lethargy	Not drug induced	+4	3	6	1
Ear pain	Acute onset	-3	0	1	1
Non-exudative pharyngitis	Acute onset	-3	0	1	1
Hoarseness	Acute not chronic	-3	0	0	1
Sputum (purulent)	Excluding AECB	-3	0	5	0.2489
Hemoptysis	Mild/moderate	-3	0	2	1
Chest pain (pleuritic)	Acute onset	-3	0	0	1
Loose stools/watery diarrhea	Not drug induced	+3	2	2	0.5327
Abdominal pain	With/without diarrhea	+1	0	0	1
Renal failure	Acute (not chronic)	+3	4	9	1
Shock/hypotension	Excluding cardiac/pulmonary causes	-5	0	7	0.1013
Splenomegaly	Excluding non-CAP causes	-5	0	0	1
Lack of response to β-lactam antibiotics	After 72 h (excluding viral pneumonias)	+5	2	2	0.5327
Laboratory features					
Chest X-ray	Rapidly progressive asymmetric infiltrates	+3	5	12	1
Severe hypoxemia with A-a gradient > 35	Acute onset	-5	3	13	0.0654
Hyponatremia	Acute onset	+1	4	4	0.1176
Hypophosphatemia	Acute onset	+5	1	0	0.2778
AST/ALT > normal range	Acute onset	+2	3	5	0.6078
Total bilirubin > normal range	Acute onset	+1	0	6	0.1141
LDH > 400 U/L	Acute onset	-5	3	6	1
CPK > normal range	Acute onset	+4	4	4	0.1176
CRP > 30 mg/dL	Acute onset	+5	2	4	1
Cold agglutinin titer ≥ 1:64	Acute onset	-5	0	0	1
Severe relative lymphopenia (<10%)	Acute onset	+5	3	7	1
Ferritin > 2 × normal range	Acute onset	+5	3	2	0.0987
Microscopic hematuria	Excluding trauma, BPH, Foley catheter, bladder/renal neoplasms	+2	3	2	0.0987

AECB: acute exacerbation of chronic bronchitis, BPH: benign prostatic hyperplasia, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, CRP: C-reactive protein

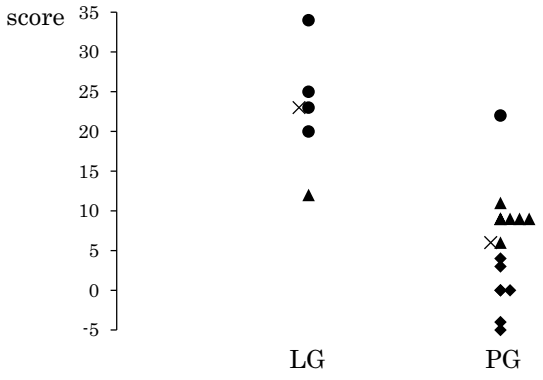

Figure. The summed scores with the WUH system. LG: Legionella group, PG: pneumococcal pneumonia group, ●: Legionella very likely, ▲: Legionella likely, ◆: Legionella unlikely, ×: median.

nation of broad spectrum β-lactam antibiotics and macrolides or quinolones. Pneumococcal pneumonia may induce the development of infective endocarditis and/or meningitis secondary to bacteremia, very severe complications that are rarely seen in LD, warranting echocardiography or spinal tap if pneumococcal pneumonia, but not LD, is strongly suspected. In these instances, clinicians should choose ceftriaxone plus vancomycin, instead of ceftriaxone plus levofloxacin. Therefore, any attempt, including the WUH system, to distinguish PG and LG is of prime importance in an encounter with patients with severe CAP. All of the cues needed for the WUH system were examined in this study, and a temperature >39℃ with relative bradycardia and headache were significantly more common in the LG. Similar results have been observed in other studies (13, 14).

In this study, the WUH system score for the LG was significantly higher than that for the PG. Our study also found that the modified WUH system had good sensitivity and specificity for diagnosing LD, although the original version first introduced in 1998 didn't have sufficient sensitivity to exclude LD (4). The modified system utilized in the present study contains more refined clinical and laboratory parameters (e.g., temperature >39℃ with relative bradycardia, shock/hypotension, elevated CRP and CPK levels) than the original version (9). The addition of these parameters to the modified system is likely to have contributed to the promising results of the current study. The newly added parameters were significantly more specific for LD than the previous parameters (15), so the system had higher sensitivity and specificity in our study than previously.

Haubitz et al. (16) published a simple prediction rule with

six dichotomized scores showing good discrimination and a high negative predictive value to rule out LD. However, their study included patients with various severities, so its diagnostic accuracy may selectively be decreased, particularly in severe CAP.

The urine antigen test is usually applied as a point-of-care test for LD (17), although the sensitivity of this rapid diagnostic test is not high enough to exclude LD (18), as observed two of our patients with false-negative results. The test turns positive within 48-72 hours of symptom onset and can remain positive for several weeks or months (6, 19). Blood and respiratory specimen cultures also have low sensitivity. Polymerase chain reaction and serological tests often allow for only delayed or post hoc diagnosis. Therefore, using the WUH system to discriminate LD from other causes on hospital admission is useful for directing the choice of appropriate antibiotic therapy, even if the urine antigen test provides a false-negative response.

Our study found that the WUH system has an advantage in specificity rather than in sensitivity in terms of diagnostic characteristics. Therefore, the WUH system, when scored very high, is useful for ruling in a diagnosis of LD, even though one patient in the PG scored a false-positive because of high point parameters. Future investigations with a larger number of patients should provide deeper insight into the clinical usefulness of this diagnostic algorithm.

Several limitations associated with the present study warrant mention. First, the data were collected retrospectively from a single university hospital. Second, the sample size was quite small. Third, the overall group of patients did not have full laboratory data available. Finally, our study did not account for the coexistence of LD and pneumococcal pneumonia. However, these limitations should not prevent the WUH system from being implemented in clinical practice.

In conclusion, the WUH system is therefore considered to be useful for providing a rapid presumptive clinical diagnosis of LD, thereby bringing about an improvement in the timing and choice of empirical antibiotic therapy for severe CAP.

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

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