J Infect Chemother xxx (2017) 1–5

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Committee Report

Diagnostic predictors of *Legionella* pneumonia in Japan☆

Naoyuki Miyashita [a, *], Nobuyuki Horita [b], Futoshi Higa [c], Yosuke Aoki [d], Toshiaki Kikuchi [e], Masafumi Seki [f], Kazuhiro Tateda [g], Nobuko Maki [h], Kazuhiro Uchino [i], Kazuhiko Ogasawara [i], Hiroshi Kiyota [j], Akira Watanabe [k]

[a] Department of Internal Medicine 1, Kawasaki Medical School, Okayama, Japan
[b] Department of Pulmonology, Yokohama City University Graduate School of Medicine, Japan
[c] National Hospital Organization Okinawa National Hospital, Japan
[d] Department of Infectious Disease and Hospital Epidemiology, Saga University Hospital, Japan
[e] Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Japan
[f] Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University Hospital, Japan
[g] Department of Microbiology and Infectious Diseases, Toho University School of Medicine, Japan
[h] Taisho Toyama Pharmaceutical Co., Ltd, Japan
[i] Daiichi Sankyo Co., Ltd, Japan
[j] Department of Urology, The Jikei University Katsushika Medical Center, Japan
[k] Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, Japan

ARTICLE INFO

Article history:
Received 8 September 2017
Received in revised form
13 November 2017
Accepted 14 December 2017
Available online xxx

Keywords:
Community-acquired pneumonia
C-reactive protein
Diagnostic predictors
Legionella
Serum sodium

1. Introduction

Community-acquired pneumonia (CAP) continues, even nowadays, to be one of the most common causes of morbidity and hospitalization worldwide. Epidemiologic studies show that in the combined cause-of-death category, pneumonia ranks third as the leading cause of death in Japan. Because of this high morbidity and mortality, the Japanese Respiratory Society (JRS) has been developing its guidelines since 1998, and updated pneumonia guidelines were published in 2017 [1]. Of pathogens that are of consequence in patients with CAP, *Legionella* and *Streptococcus pneumoniae* are the two leading causes of severe CAP and are associated with high mortality, and rapid identification of the disease-causing organism is important [1–3].

Currently available diagnostic tests include detection of *Legionella* spp. by culture, polymerase chain reaction (PCR) or loop-mediated isothermal amplification method in respiratory samples and *Legionella pneumophila* antigen testing in urine. These tests lack sensitivity, in addition the urine antigen test only identified *L. pneumophila* serogroup 1 [4]. Thus, many researchers have investigated and proposed diagnostic predictors of *Legionella* CAP, because several clinical signs and symptoms such as bradycardia, impaired consciousness and gastrointestinal symptoms are more seen in *Legionella* CAP compared with non-*Legionella* CAP [5–10]. However, the independent diagnostic predictors of *Legionella* CAP differ among reports [6–12]. The differences may result from comparison of CAP due to different causative pathogens. In addition to comparison of CAP, the sample size of the *Legionella* CAP populations in previous studies were small.

The aim of this study was to analyze initial clinical and laboratory parameters with a larger *Legionella* CAP population and compare them with different types CAP patients with *S. pneumoniae*, which is the most common form of bacterial CAP, and *Mycoplasma pneumoniae*, which is the most common atypical pneumonia [1] and thereby to identify reliable diagnostic predictors of *Legionella* CAP.

2. Materials and methods

2.1. Study population

In 2006, the Japanese Society for Chemotherapy (JSC) inaugurated a *Legionella* Committee to improving the management of

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Department of Internal Medicine 1, Kawasaki Medical School, 2-6-1 Nakasange, Kita-ku, Okayama City, Okayama, 700-8505, Japan.
E-mail address: nao@med.kawasaki-m.ac.jp (N. Miyashita).

https://doi.org/10.1016/j.jiac.2017.12.009

Legionella CAP. Between December 2006 and November 2011, 176 cases of *Legionella* CAP were recorded throughout Japan [13]. A complete list of participating facilities is provided in the appendix. For comparison we used 217 cases of *S. pneumoniae* CAP and 202 cases of *M. pneumoniae* CAP who were diagnosed during study period. Cases of pneumonia mixed with other microorganisms were excluded from this study. To identify diagnostic predictors of *Legionella* CAP, we used baseline parameters as reported previously [13]. The study protocol was approved by the Ethics Committee at Kawasaki Medical School.

2.2. Statistical analysis

To estimate the potential clinical relevance of clinical and laboratory parameters to diagnose *Legionella* CAP, we used likelihood-ratio tests and univariate and multivariate logistic regression models. Thereby, outcomes were either *Legionella* CAP or non-*Legionella* CAP. For all independent variables in multivariate analysis, we calculated receiver-operating-characteristics (ROC) with the area under the ROC curve (AUC) being an overall diagnostic measure. The contribution of each potential predictors was denoted by an odds ratio (OR) and associated 95% confidence interval (CI).

3. Results

3.1. Clinical predictors of Legionella CAP when the comparison CAP was S. pneumoniae

To assess the diagnostic reliability of clinical signs, symptoms and laboratory parameters to identify *Legionella* CAP patients, we calculated univariate logistic regression analysis (Table 1) with all parameters that were significantly different between *Legionella* and *S. pneumoniae* CAP patients on presentation. Furthermore, to identify independent predictors of *Legionella*, we calculated multivariate logistic regression analysis (Table 1).

Multivariate analysis identified four clinical parameters: dyspnea (OR 6.26, 95% CI 3.36–11.67, $p < 0.001$), absence of cough (OR 0.24, 95% CI 0.10–0.57, $p = 0.0013$); male (OR 3.56, 95% CI 1.69–7.49, $p < 0.001$); and current smoking history (OR 3.01, 95% CI 1.48–6.12, $p = 0.0023$), and three laboratory parameters: C-reactive protein (CRP) (OR 1.07, 95% CI 1.04–1.11, $p < 0.001$); sodium (OR 0.87, 95% CI 0.81–0.93, $p < 0.001$); and lactate dehydrogenase (LDH) (OR 1.05, 95% CI 1.02–1.08, $p = 0.0022$) as independent predictors of *Legionella* CAP.

3.2. Clinical predictors of Legionella CAP when the comparison CAP was M. pneumoniae

Multivariate analysis identified five clinical parameters: age (OR 1.09, 95% CI 1.05–1.14, $p < 0.001$); dyspnea (OR 13.30, 95% CI 3.29–53.76, $p < 0.001$); absence of cough (OR 0.02, 95% CI 0.01–0.18, $p < 0.001$), male (OR 5.81, 95% CI 1.16–29.08, $p = 0.007$); and mental manifestation (OR 62.51, 95% CI 2.99–1308.98, $p = 0.007$), and three laboratory parameters: CRP (OR 1.18, 95% CI 1.09–1.28, $p < 0.001$); WBC count (OR 1.05, 95% CI 1.03–1.08, $p < 0.001$); and sodium (OR 0.81, 95% CI 0.70–0.95, $p < 0.001$) as independent predictors of *Legionella* CAP (Table 2).

3.3. Clinical predictors of Legionella CAP when the comparison CAP was both S. pneumoniae and M. pneumoniae

Multivariate analysis identified four clinical parameters: dyspnea (OR 6.41, 95% CI 3.52–11.67, $p < 0.001$); absence of cough (OR 0.21, 95% CI 0.09–0.47, $p < 0.001$); male (OR 3.79, 95% CI 1.84–7.77, $p < 0.001$); and current smoking history (OR 3.04, 95% CI 1.56–5.93, $p < 0.001$), and three laboratory parameters: LDH (OR 1.05, 95% CI 1.02–1.08, $p < 0.001$); CRP (OR 1.08, 95% CI 1.05–1.12, $p < 0.001$); and sodium (OR 0.85, 95% CI 0.80–0.91, $p < 0.001$) as independent predictors of *Legionella* CAP (Table 3).

4. Discussion

In this study, we analyzed the clinical and laboratory parameters of a large sample population with *Legionella* CAP and compared them with different CAP types, comprising the most common bacterial pneumonia and atypical pneumonia. Predictably, we found differences in the diagnostic predictors of *Legionella* CAP when the different causative pathogens were compared.

Fiumefreddo and colleagues identified six clinical and laboratory parameters, comprising high body temperature (>39.4 °C), high levels of CRP (>187 mg/L), high levels of LDH (>225 mmol/L), low platelet counts (<171 × 10^9/L), low serum sodium concentration (<133 mmoL/L), and absence of sputum production, as independent predictors of *Legionella* CAP [11]. The ROC showed a high diagnostic accuracy for this diagnostic score with an AUC of 0.86 [11]. Haubitz and colleagues also showed excellent discrimination of these six parameters with an AUC of 0.91 (95% CI, 0.87–0.94) [12]. The results from multivariate analysis from three studies on six clinical parameters for predict *Legionella* CAP are summarized in Table 4.

Among the six parameters, two parameters, namely high levels of CRP (>187 mg/L) and low serum sodium concentration (<133 mmoL/L), showed reproducibility in all three studies (Table 4). To estimate the clinical usefulness of these parameters, ROC curves using the six original parameters and the two reproducible parameters in the three studies, CRP and sodium, were calculated (Fig. 1). The AUC of diagnostic scores were almost identical between two methods with 0.84 (95% CI, 0.80–0.87, $p < 0.001$) in six original parameters and 0.84 (95% CI, 0.81–0.88, $p < 0.001$) in two reproducible parameters. Thus, CRP and sodium may be good diagnostic predictors of *Legionella* CAP not only in Western countries but also in Japan.

The remaining two parameters among the six original parameters, high levels of LDH and high body temperature, showed reproducibility in two studies including our study. In our study, discrepancy results were observed with these two parameters between the comparison CAP due to *S. pneumoniae* and *M. pneumoniae*. LDH was identified in *S. pneumoniae* CAP but not identified in *M. pneumoniae* CAP by multivariate analysis. Body temperature was identified in *S. pneumoniae* CAP but not identified in *M. pneumoniae* CAP by univariate analysis. It is well known that one of clinical features of *M. pneumoniae* CAP is high fever [14,15]. Thus, high body temperature was not a reliable diagnostic predictor of *Legionella* CAP when the comparison CAP was *M. pneumoniae*.

Low platelet counts and absence of sputum production showed no reproducibility. These parameters were only identified in the original study [11], and our result supported the Haubitz's result [12]. In particular, low platelet counts were not identified in either the univariate analysis or multivariate analysis in both studies.

Male, current smoking history, dyspnea, and absence of cough were newly identified as independent predictors of *Legionella* CAP in our study. It is well known that one of clinical features of *M. pneumoniae* CAP is paroxysmal cough [14,15]. Thus, the absence of cough might be affected by *M. pneumoniae* CAP. Discrepancy in the results were observed in current smoking history in the comparison of CAP due to *S. pneumoniae* and *M. pneumoniae*. This parameter was identified in *S. pneumoniae* CAP but not in *M. pneumoniae* CAP using the multivariate analysis. The remaining two parameters were possibility of peculiar to Japanese patients because these parameters showed no differences in the comparison

Please cite this article in press as: Miyashita N, et al., Diagnostic predictors of *Legionella* pneumonia in Japan, J Infect Chemother (2017), https://doi.org/10.1016/j.jiac.2017.12.009