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Original Article

β2 microglobulin and lactate dehydrogenase are indices of different features of *Mycoplasma pneumoniae*-associated community-acquired lower respiratory tract infection for severity evaluation in children☆

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ABSTRACT

Using the hospital records, we retrospectively assessed whether urinary β2 microglobulin/creatinine ratio (UBCR) and lactate dehydrogenase (LD) values could be used to estimate the severity of *Mycoplasma pneumoniae*-associated lower respiratory tract infection (MP-LRTI). We studied 48 patients with MP-LRTI (median age, 7.5 years; range, 3–14 years) admitted to Kagoshima City Hospital and examined the relationships of the UBCR or LD values with fever and pulmonary tissue damage (hypoxemia and severity assessments on chest radiographs). Patients were assigned to four groups based on whether they had fever and/or hypoxemia. Patients with high fever showed significantly higher UBCR values than those without ($P < 0.05$), whereas those with hypoxemia showed higher LD values than those without ($P = 0.001$). The maximum body temperature on admission was closely associated with the UBCR but not with LD levels. In chest radiography assessments, LD levels were significantly higher in patients with severe than mild or moderate MP-LRTI. A cut-off LD level of 530 IU/L showed a very high sensitivity (100%) and specificity (93%). Although UBCR values were higher in patients with severe MP-LRTI, the differences were not statistically significant. Our study shows that the UBCR is associated with body temperature, whereas LD levels may serve as an index of pulmonary tissue damage in children with MP-LRTI.

1. Introduction

Mycoplasma pneumoniae (MP) is an important cause of community-acquired lower respiratory tract infection (LRTI). The pathology of MP-associated LRTI (MP-LRTI) is attributable to host immune reaction. T helper-1 cytokines are likely activated by and associated with the activation of cell-mediated immunity [1–3]. Regarding MP-LRTI treatment, various recommendations on the use of antimicrobial agents or steroids have been reported. Prolonged fever following steroid treatment in MP pneumonia has also been reported [4], suggesting that steroid therapy is not necessarily effective in shortening the duration of fever. Thus, separate evaluation of fever and pulmonary tissue damage in patients with MP-LRTI would ensure effective treatment.

Serum lactate dehydrogenase (LD) levels are reported to be useful in evaluating the severity of MP pneumonia [3,5–9], but studies have not separately examined parameters indicating systemic inflammatory reaction, like fever, or those indicating pulmonary tissue damage. β2 microglobulin (β2MG) levels have also been reported to be elevated in patients with severe MP pneumonia [10,11], but there is no description of the relationship between high β2MG levels and MP pneumonia severity. An MP infection outbreak occurred in Kagoshima city from 2015 to 2016, and several patients with MP-LRTI were admitted to Kagoshima City Hospital. Patients with high fever on admission without hypoxemia or severe MP pneumonia showed high β2MG values, suggesting the association of β2MG values with fever.

Therefore, we investigated whether β2MG and LD levels can be used to evaluate the severity of MP-LRTI compared to fever or parameters indicating pulmonary tissue damage.

Abbreviations: UBCR, β2 microglobulin/creatinine ratio; LD, lactate dehydrogenase; MP-LRTI, *Mycoplasma pneumoniae*-associated lower respiratory tract infection; MP, *Mycoplasma pneumoniae*; LRTI, lower respiratory tract infection; β2MG, β2 microglobulin; LAMP, loop-mediated isothermal amplification; CRP, C-reactive protein; IFNγ, interferon gamma.

☆ All authors meet the ICMJE authorship criteria.

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2. Patients and methods

2.1. Patient selection

MP infection in Kagoshima city reached epidemic levels in June 2015, and 96 patients with MP-LRTI were admitted to Kagoshima City Hospital between October 2015 and December 2016. MP-LRTI diagnosis was based on clinical symptoms, such as fever and no productive cough, as well as chest radiography findings [12]. All 96 patients were positive for a rapid MP test using the loop-mediated isothermal amplification (LAMP) method (Loopamp® Mycoplasma P detecting reagent kit; Eiken Chemical Co., Ltd., Tokyo, Japan) and a throat swab.

We excluded patients showing recurrent fever after symptom alleviation due to treatment prescribed by a previous physician, those with an underlying disease affecting renal function; those with one influencing pulmonary or respiratory functions, such as bronchial asthma, chronic pulmonary disease, congenital heart disease, severe obesity, or immunodeficiency; and those who had ever received systemic steroids. Patients <3 years old were excluded because of the increased prevalence of viral respiratory infections in this age group and because individuals of this age group often mount a weak immune reaction. Patients with fever lasting <5 days before admission were excluded on the basis of a study which showed that fever was alleviated within 2–3 days after the administration of effective antimicrobial agents [13]. Also, patients with ≥5 days of fever are often considered for hospitalization in our institution. Thus, 48 patients were finally included in this study.

The study design was approved by the appropriate ethics review board, and informed consent was waived because of the retrospective nature of the study.

2.2. β2MG and LD measurements

Urinary β2MG levels were determined by measuring the urinary β2MG/creatinine ratio (UBCR) in a spot urine test on the day of or day after admission. Because renal dysfunction could affect β2MG levels, we evaluated the serum creatinine levels of all patients and determined that no patient had renal dysfunction. Using normal values in kidney disease [14,15] as reference, a UBCR value of 500 μg/gCr or lower was adopted as normal.

LD values were excluded when 2 + or higher hemolysis was noted, to avoid the effect of sampling-induced hemolysis. An LD value of 222 IU/L was regarded as normal on the basis of normal values measured during in-hospital examination.

2.3. Evaluation of disease severity

Hypoxemia and assessment of severity on chest radiographs were considered as indices of pulmonary tissue damage.

We used the maximum body temperature within 24 h after admission and the lowest SpO_2 as the SpO_2 value, as hypoxemia can occur during night sleep.

The criteria for high fever were those used for the systemic inflammatory response syndrome [16] in children, i.e., a body temperature of 38.5 °C or higher. Goldstein et al. [16] used a core temperature, but in this study, we used in-hospital axillary temperatures. An SpO_2 of 92% or lower, which is the criterion for oxygen administration, was regarded as hypoxemia. For severity assessments on chest radiographs, in addition to the classification proposed by Ouchi et al. [17], lesion laterality was included in the evaluation. Unilateral infiltration shadows accounting for up to 2/3 or more of one side were evaluated as mild or moderate, respectively, whereas bilateral infiltration with a total area accounting for up to 2/3 or more of one side was evaluated as moderate or severe, respectively. According to these criteria, patients were grouped as follows: Group A, patients without high fever or hypoxemia (N = 17); Group B, patients with high fever but without hypoxemia (N = 17); Group C, patients without high fever but with hypoxemia (N = 5); and Group D, patients with both high fever and hypoxemia (N = 9).

2.4. Statistical analysis

All statistical analyses were performed by EZR (Saitama Medical Center, Jichii Medical University, Saitama, Japan; http://www.jicni.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html;Kanda,2012). The significance level was set at a 2-sided value of 5%. Kruskal–Wallis and Steel–Dwass tests were used to compare the UBCR or LD levels among groups and for different chest radiography severity degrees. Spearman's rank correlation coefficient was used to compare the maximum body temperature and the values of UBCR or LD. The optimal cut-off value for each test was analyzed using the receiver operating characteristic curve, and the values showing the highest sensitivity and specificity were adopted. Since both UBCR and LD assessments yielded extreme outlier values, we $\log_{10}$-transformed the data and created a normal QQ plot for confirmation. The distribution was nearly normal for both UBCR and LD values, so the outliers were not excluded.

3. Results

3.1. Clinical symptoms and laboratory data on admission

The median age of the 48 patients was 7.5 (3–14) years, and 31 patients (65%) were boys. The median duration of fever before admission was 7 (5–12) days (Table 1).

White blood cell counts at admission varied, but the percentage of neutrophils was 50% or higher in all patients. The incidence of raised C-reactive protein (CRP) levels was not always high, and the median level was 2.47 mg/dL (Table 1).

3.2. UBCR and LD values in each group

The UBCR was significantly higher in Groups B and D than in Group A (P = 0.03 and 0.01, respectively; Fig. 1A). Notably, patients in both Group B and D had high fever. The UBCR was measured for only two patients in Group C, thus we could not make a sufficient evaluation in comparison with this group. LD values in group D were significantly higher than those in group A (P = 0.009; Fig. 1B). The difference was not statistically significant among other groups, but LD values in patients with hypoxemia (Group C and D) were higher than those without hypoxemia (P = 0.001).

3.3. Relationships between the UBCR or LD values and the maximum body temperature on admission

The maximum body temperature on admission and UBCR values showed a significantly high correlation (Fig. 2A), whereas, LD values showed no significant relationship with body temperature (Fig. 2B).

3.4. Comparison of the UBCR or LD values according to severity assessments on chest radiographs

UBCR values in severe cases were higher than those in mild cases, but the difference was not statistically significant (Fig. 3A). In contrast, LD levels were significantly higher in severe than in mild or moderate cases (Fig. 3B). The area under the receiver operating

Table 1
Clinical symptoms and laboratory data on admission.

	Number, median age	
Group A	17 (male, 9; female, 8), median age 9 (5–13)	
Group B	17 (male, 11; female, 6), median age 6 (3–13)	
Group C	5 (male, 4; female, 1), median age 4 (3–6)	
Group D	9 (male, 8; female, 1), median age 8 (4–14)	
	Median or average values	
WBC (/μl) (N = 48)	7529 ± 2887	
Neutrophil (%) (N = 46)	70.7 ± 10.2	
CRP (mg/dL) (N = 48)	2.47 (0.30–21.07)	
AST (IU/L) (N = 48)	32 (23–106)	
LD (IU/L) (N = 46)	330 (184–1098)	
Na (mEq/L) (N = 48)	135.8 ± 3.3	
UBCR (μg/gCr) (N = 30)	678 (127–120,711)	
	Median values (range)	
	UBCR (μg/gCr)	LD (IU/L)
Group A	208 (127–8464) (N = 12)	289 (184–404) (N = 17)
Group B	1.424 (262–18,762) (N = 9)	337 (217–632) (N = 16)
Group C	4364 (441–8287) (N = 2)	388 (294–619) (N = 4)
Group D	10,578 (504–120,711) (N = 7)	530 (286–1098) (N = 9)

Group A; patients without high fever or hypoxemia. Group B; patients with high fever but without hypoxemia. Group C; patients without high fever but with hypoxemia. Group D; patients with both high fever and hypoxemia. High fever was indicated by a body temperature of 38.5 °C or higher and hypoxemia by an SpO_2 of 92% or lower. WBC, white blood cells; CRP, C-reactive protein; AST, aspartate aminotransferase; LD, lactate dehydrogenase; Na, sodium; UBCR, urinary β2 microglobulin/creatinine ratio. Median values are shown including range (minimum-maximum). Average values are shown as means ± SD.

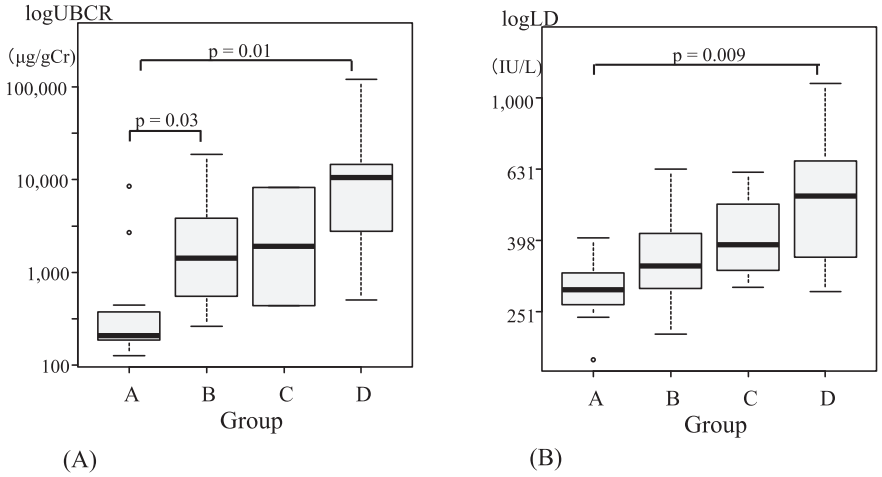

Fig. 1. β2 microglobulin/creatinine ratio (UBCR) and lactate dehydrogenase (LD) values in each group. Group A, patients without high fever or hypoxemia; Group B, patients with high fever but without hypoxemia; Group C, patients without high fever but with hypoxemia; Group D, patients with both high fever and hypoxemia. The UBCR and LD levels were log_{10}-transformed. Each box shows the first to third quartile; the horizontal center line shows the median; and the whiskers show the minimum and maximum values within 1.5 times the interquartile range. The white circles show outliers. Values on the vertical axis are back-transformed to the original data. P-values were obtained using Kruskal–Wallis and Steel–Dwass tests.

characteristic curve (AUC) of LD levels for patients with severe chest radiography findings was 0.99, indicating a very high predictive validity for this index. A cut-off LD level of 530 IU/L showed very high sensitivity and specificity of 100% and 93%, respectively. In addition, in patients with both moderate chest radiography findings and hypoxemia, a cut-off LD level of 409 IU/L showed 100% sensitivity and 90% specificity.

4. Discussion

Our study indicated that the UBCR and LD values can be used as indices of different features of MP-LRTI in children. Specifically, the UBCR was an index of fever, whereas LD values indicated pulmonary tissue damage.

The UBCR was significantly higher in the groups with high fever than those without and highly correlated with the maximum body temperature on admission, confirming its association with fever. High levels of IL-18 [2,3,6,7] and interferon gamma (IFNγ) [18,19] have been reported in patients with severe MP pneumonia. IL-18 increases IFNγ levels, and IFNγ increases MHC class 1 expression, as well as the production of β2MG, a component of MHC class 1. In a recent study, inflammasomes were thought to play an important role in MP-induced inflammation, and the authors reported that MP induces IL-1β secretion from host cells through the root via inflammasomes [20]. IL-1β is an endogenous pyrogen. Activated inflammasomes promote IL-1β and IL-18 secretion [21]. IL-1β [22] and IL-18 [3,5] levels increase from the acute to the convalescent phase in patients with community-acquired MP pneumonia. Thus,

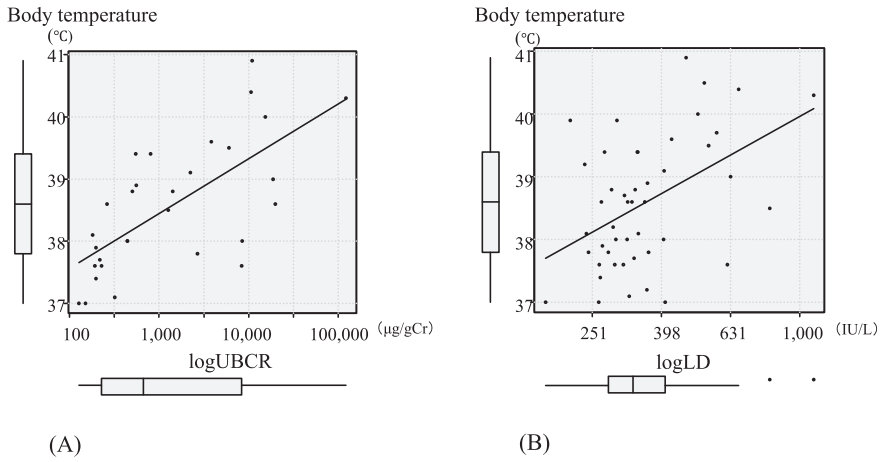

Fig. 2. Relationship between urinary β2 microglobulin/creatinine ratio (UBCR) or lactate dehydrogenase (LD) values and the maximum body temperature on admission. Spearman's rank correlation rho is 0.71 for the UBCR (A; $p < 0.001$) and 0.40 for LD values (B; $p = 0.005$).

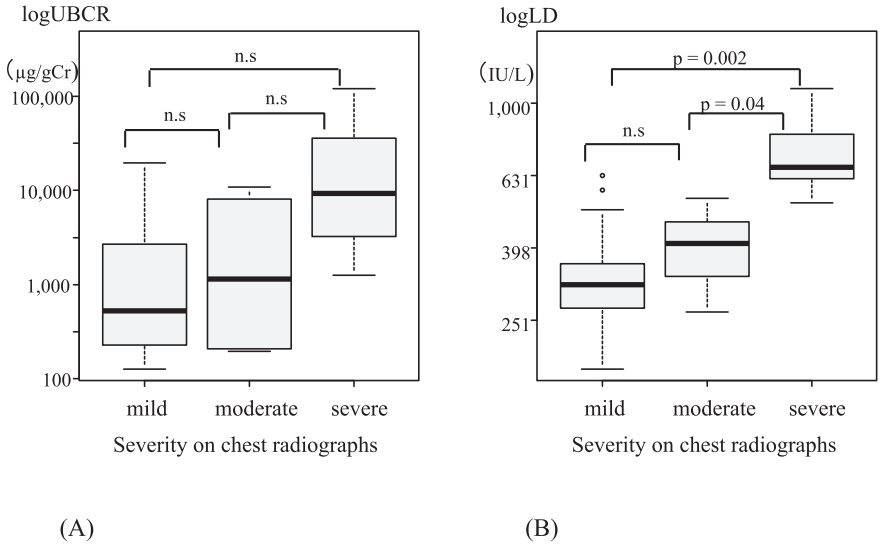

Fig. 3. Comparison of the (A) urinary β2 microglobulin/creatinine ratio (UBCR) or (B) lactate dehydrogenase (LD) values according to severity assessment on chest radiographs. The UBCR and LD levels were $\log_{10}$-transformed. Each box shows the first to third quartile; the horizontal center line shows the median; and the whiskers show the minimum and maximum values within 1.5 times the interquartile range. The white circles show outliers. Values on the vertical axis are back-transformed to the original data. P-values were obtained using Kruskal–Wallis and Steel–Dwass tests. n.s, not statistically significant.

the simultaneous release of IL-1β and IL-18 may explain the significant correlation between the UBCR and fever. Moreover, MP bacterial load was significantly higher in patients with refractory than with non-refractory MP pneumonia [18,23]. Since it leads to the production of IL-1β and IL-18, it is possible that high fever and high UBCR correlate with high MP bacterial load. Therefore, the UBCR and body temperature may be useful in evaluating the degree of immune reaction related to MP infection. Patients having prolonged but low fever or low UBCR values, may require no change in treatment or outpatient treatment. However, patients with prolonged high fever or high UBCR values, may require careful observation due to the possible exacerbation of MP pneumonia.

LD values were significantly higher in the groups with hypoxemia than those without. Furthermore, the AUC of LD levels was high in patients with severe chest radiography findings, confirming that LD values are useful in evaluating pulmonary tissue damage, consistent with previous reports. A previous report indicated that the degree of correlation between IL-18 and LD was not strong, despite being statistically significant [7,9], which might explain why LD values did not highly correlate with the maximum body temperature on admission in our study.

In patients with severe chest radiography findings, the cut-off LD level was 530 IU/L, and all patients had hypoxemia. In patients with both moderate findings and hypoxemia, the cut-off LD level was 409 IU/L. Previously, the cut-off LD level for the use of steroids in children with MP pneumonia was investigated in two studies, with a small number of patients, and was found to be 436.5 IU/L [6] and 410 IU/L [7]. Chest radiography findings are difficult to use for quantitative evaluation and are impossible to obtain frequently because of the radiation exposure. In contrast, LD values are useful for evaluating the severity of chest radiograph findings at a given time but cannot necessarily predict the subsequent severity of MP pneumonia. In order to predict severity, follow up of subsequent changes in LD values will be needed. This study suggests that when LD levels exceed 409 IU/L, the patient should be carefully monitored, and when levels continue to increase to 530 IU/L, despite the administration of adequate antimicrobial agents, re-evaluation of respiratory conditions, such as blood gas analysis, or severity of the

findings on chest radiography are necessary. Furthermore, when exacerbation of the respiratory condition is predicted, steroid therapy should be considered [6–9,11,24].

In this study, the AUC of LD levels was 0.99 in patients with severe chest radiography findings, indicating a very high predictive validity for this index. Both IL-18 and tumor necrosis factor α levels were reported to positively correlate with the number of affected pulmonary lobes [3]. In addition, patients with an aggravated disease course show bilateral diffuse infiltration shadows [10]. Thus, we classified pulmonary lesions on chest radiography as unilateral and bilateral, which may account for the high predictive validity found in our study compared to previous reports [6,7].

Our study had some limitations. First, owing to the retrospective nature of our study, we could not completely rule out other causes of respiratory infection in all subjects. All cases tested for respiratory syncytial virus, human metapneumovirus and influenza virus were negative. The records indicated that throat swabs and blood cultures were not used in most cases, and serological tests were not used in all cases. However, the positive values in the LAMP test were confirmed after diagnosis based on the clinical symptoms and chest radiography findings during the epidemic period. Additionally, to reduce the impact of viral respiratory infections, we excluded patients <3 years old. Therefore, we could conclude that the diagnosis was reliable. Second, not all patients underwent assessment of both the UBCR and LD values. For example, we could not make a sufficient evaluation of the UBCR in group C, which included only two children. Thus, further studies are necessary including a greater number of cases. Third, LD levels vary with age, and this was not taken into consideration in the current study. Therefore, in future studies, LD values should be age-adjusted.

5. Conclusions

The UBCR and LD values may serve as indices of fever and pulmonary tissue damage, respectively, in children with MP-LRTI. Separate evaluation of fever and pulmonary tissue damage may be important to ensure adequate treatment.

Declaration of interest

None.

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