# Usefulness of β-lactam and Macrolide Combination Therapy for Treating Community-acquired Pneumonia Patients Hospitalized in the Intensive Care Unit: Propensity Score Analysis of a Prospective Cohort Study

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# Abstract

**Background:** Previous studies reported that β-lactam and macrolide combination therapy significantly improved outcomes for patients with severe community-acquired pneumonia hospitalized in the intensive care unit (ICU) compared with a non-macrolide regimen. However, whether β-lactam and macrolide therapy truly reduces mortality is controversial, because no randomized, controlled trials have been conducted. The aim of the present study was to evaluate the usefulness of β-lactam and macrolide combination therapy for severe community-acquired pneumonia patients hospitalized in the ICU compared with a non-macrolide β-lactam-containing regimen.

**Methods:** A prospective, observational, cohort study of hospitalized pneumonia patients was performed. Hospitalized severe community-acquired pneumonia patients admitted to the ICU within 24 hours between October 2010 and October 2017 were included for analysis. The primary outcome was 30-day mortality, and secondary outcomes were 14-day mortality and ICU mortality. Inverse probability of treatment weighting analysis as a propensity score analysis was used to reduce biases, including six covariates: age, sex, C-reactive protein, albumin, Pneumonia Severity Index score, and APACHE II score.

**Results:** A total of 78 patients were included. There were 48 patients in the non-macrolide-containing β-lactam therapy group, including β-lactam monotherapy and β-lactam and non-macrolide-containing combination therapy, and 30 patients in the macrolide combination therapy group. β-lactam and macrolide combination therapy significantly decreased 30-day mortality (16.7% vs. 43.8%; *P*=0.015) and 14-day mortality (6.7% vs. 31.3%; *P*=0.020), but not ICU mortality (10% vs 27.1%, *P*=0.08) compared with non-macrolide-containing β-lactam therapy. After adjusting by inverse probability of treatment weighting, macrolide combination therapy also decreased 30-day mortality (odds ratio, 0.29; 95%CI, 0.09-0.96; *P*=0.04) and 14-day mortality (odds ratio, 0.19; 95%CI, 0.04-0.92; *P*=0.04), but not ICU mortality (odds ratio, 0.34; 95%CI, 0.08-1.36; P=0.13).

**Conclusions:** Combination therapy with β-lactam and macrolides significantly improved the prognosis of severe community-acquired pneumonia patients hospitalized in the ICU compared with a non-macrolide-containing β-lactam regimen on propensity score analysis.

**Trial registration:** UMIN Clinical Trials Registry, UMIN000004353. Registered on 7 October 2010,

# Background

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality among infectious diseases worldwide [1]. Severe CAP (SCAP) patients hospitalized in the intensive care unit (ICU) are reported to have a high mortality of up to 25–50% [2–4]. To improve the prognosis of SCAP patients, comprehensive treatment including antimicrobial therapy, mechanical ventilatory support, vasopressor drug support, and nutrition is essential, and early and appropriate antibiotic therapy is particularly important [5, 6].

Some CAP guidelines recommend that β-lactam combination therapy including β-lactam and macrolides or β-lactam and quinolones should be administered to SCAP patients hospitalized in the ICU [1, 7]. Many previous studies have reported that β-lactam and macrolide combination therapy (macrolide combination therapy) was useful for reducing mortality in SCAP patients compared with β-lactam monotherapy or β-lactam and quinolones [8–13]. However, these were all prospective cohort studies including prospective and retrospective parts, and there have been no randomized, controlled trials (RCTs) that definitively showed the clinical usefulness of macrolide combination therapy so far. In addition, Adrie et al showed that dual therapy including β-lactam plus macrolide or fluoroquinolone did not significantly reduce 60-day mortality compared with β-lactam monotherapy for CAP patients requiring ICU admission [14]. Therefore, whether macrolide combination therapy truly improves the prognosis of SCAP patients compared with other regimens is still controversial. Furthermore, all previous studies that showed the usefulness of macrolide combination therapy were conducted in the United States and in European countries, and no study was conducted in other areas or countries, including Asian countries.

The aim of the present study was to investigate whether macrolide combination therapy significantly reduced the mortality of SCAP patients hospitalized in the ICU compared with a non-macrolide-containing antibiotic regimen. Propensity score analysis was used to reduce some biases.

# Methods

Study design and setting

This observational, prospective cohort study enrolled consecutive patients with pneumonia, including CAP and healthcare-associated pneumonia (HCAP), hospitalized at the Kurashiki Central Hospital, which is a 1,166-bed tertiary hospital, between October 2010 and October 2017. The patients were diagnosed as having pneumonia based on the Infectious Diseases Society of America/American Thoracic Society guidelines [1]. Briefly, patients were diagnosed as having pneumonia if they had at least one of the following clinical symptoms (fever, cough, sputum, dyspnea, and pleuritic chest pain), plus at least one finding of coarse crackles on auscultation or elevated inflammatory biomarkers including C-reactive protein or white blood cell count, in addition to new infiltrates on chest radiography. Patients with CAP hospitalized in the ICU within 24 hours of admission were included. The exclusion criteria were age < 15 years, HCAP [15], hospital-acquired pneumonia, and patients treated without a β-lactam. Patients diagnosed with *Legionella* pneumonia on admission were also excluded because they were all treated with fluoroquinolones or macrolides and not treated with a β-lactam. This study was performed as a clinical study of pneumonia (UMIN000004353) and was approved by the institutional review board of Kurashiki Central Hospital (approval number 3398). Based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, the research subjects were notified or the public was made aware of information concerning the research on a website. All patients gave their informed consent to participate in this study by being given opportunities to refuse to participate.

In all patients, pneumonia severity on admission was assessed using the CURB-65 score [confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths per minute, low blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg), and age ≥ 65 years] [16] and the Pneumonia Severity Index (PSI) [17]. The APACHE II score, which was previously reported to be able to predict prognosis well in ICU patients, was also evaluated [18]. The antibiotics administered to all patients were at the discretion of the attending physician.

Criteria for admission to the intensive care unit and patient management

Pneumonia patients were usually treated in the ICU on admission if at least one of the following criteria was met: (1) need for mechanical ventilatory support including non-invasive positive pressure ventilation and invasive positive pressure ventilation; (2) need for vasopressor drug therapy; or (3) unstable condition that would lead to mechanical ventilatory support or vasopressor drug support early, although the patients did not need such support on admission.

In our hospital, a semi-closed ICU system was adopted. In brief, a member of the Department of Respiratory Medicine was the attending physician of hospitalized CAP patients in the ICU and selected the antibiotic regimen. On the other hand, intensivists provided comprehensive patient care, including management of mechanical ventilation, circulatory dynamics, and nutrition.

Antibiotic regimens

The non-macrolide-containing therapy group (non-macrolide group) was defined as including β-lactam monotherapy or β-lactam + non-macrolide antibiotic (quinolones, tetracyclines, glycopeptides) combination therapy. The macrolide combination group was defined as including β-lactam + macrolides or β-lactam + macrolides + other antibiotics. De-escalation and the duration of antimicrobial agent treatment were at the discretion of the attending physicians.

Microbiologic examinations

Sputum and blood for cultures and blood for measuring serum antibodies were collected on admission to detect causative pathogens. A causative microorganism was identified according to a previous report [19].

In summary, a causative pathogen was identified if any one of the following criteria was satisfied: (1) positive sputum culture of more than 1 + on a qualitative test or ≥ $10^5$ on a quantitative test, in the context of a significant Gram stain; (2) positive blood culture, excluding bacterial contamination; (3) positive pleural fluid culture; (4) positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila* serogroup 1; (5) seroconversion or a 4-fold increase in the antibodies for *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*; and (6) ≥ 1:320 on single particle agglutination antibody test for *M. pneumoniae*

(FUJIREBIO; Tokyo, Japan) or ≥ 2.0 the cut-off index on a *C. pneumoniae* IgM antibody test (Hitazyme assay; Hitachi Chemical, Tokyo, Japan).

Outcomes

The primary outcome of this study was 30-day mortality, and secondary outcomes were 14-day mortality and ICU mortality.

# Statistical analysis

Nominal variables are expressed as numbers and percentages, whereas continuous variables are expressed as medians and interquartile range. Nominal variables were analyzed using Fisher's exact test, and continuous variables were analyzed using the non-parametric Mann-Whitney U-test.

For comparisons of 30-day mortality, 14-day mortality, and ICU mortality between the non-macrolide group and the macrolide combination group, propensity score (PS) methods were used to reduce bias and the effects of patients' confounding factors on the treatment outcomes. The PS was defined as the probability that a patient would be assigned to a particular therapy, based on the patients' baseline covariates. Inverse probability of treatment weighting (IPTW) was selected for PS analysis, because it was reported to result in a lower mean squared error when estimating the effect of treatment [20]. The PS was estimated by multivariate logistic regression analysis involving six covariates, including age, sex, C-reactive protein, albumin, PSI score, and APACHE II score. These covariates were selected based on previous reports analyzing prognostic factors for CAP patients in the ICU [21–24]. All statistical analyses were two-tailed, and a *P* value of < 0.05 was considered significant. Analyses were conducted by R (version 3.0.3, Vienna, Austria).

# Results

Patients' characteristics

In this prospective cohort, a total of 1,544 CAP patients were hospitalized, and 78 patients were finally included in the analysis (Fig. 1). Table 1 shows the baseline characteristics of the non-macrolide group and the macrolide combination group. The two groups did not differ significantly in age, sex, comorbidities, vital signs, or laboratory examinations on admission. Of the indices of pneumonia severity, only the PSI score was significantly different between the groups, and the CURB-65 and APACHE II score showed no significant differences. The rates of mechanical ventilatory support and vasopressor drug support were not significantly different between the two groups. The 30-day mortality rate and the 14-day mortality rate were significantly lower in the macrolide combination group than in the non-macrolide group (16.7% vs. 43.8%, *P* = 0.015; 6.7% vs. 31.3%, *P* = 0.020), but not the ICU mortality rate (10% vs. 27.1%, *P* = 0.08) (Fig. 2). There were 0 and 5 deaths within 30 days of admission in the macrolide combination and non-macrolide groups, respectively. These patients were transferred to a medical ward from the ICU because a do not attempt resuscitation order was issued in the ICU based on the determination that no further recovery was likely.

Table 1
Patients' characteristics

| | All patients<br>n = 78 | Non-macrolide-<br>containing group[a]<br>n = 48 | Macrolide combination group<br>n = 30 | P value |
|---|---|---|---|---|
| Age (y) | 75 [66−81] | 76 [72−81] | 70 [60−82] | 0.14 |
| Male | 58 (74.4) | 37 (77.1) | 21 (70.0) | 0.60 |
| Comorbidities | | | | |
| COPD[b] | 31 (39.7) | 22 (45.8) | 9 (30.0) | 0.24 |
| Chronic heart disease | 22 (28.2) | 15 (31.3) | 7 (23.3) | 0.61 |
| Diabetes mellitus | 15 (19.2) | 10 (20.8) | 5 (16.7) | 0.77 |
| Malignant disease | 9 (11.5) | 6 (12.5) | 3 (10.0) | 1.00 |
| Chronic kidney disease | 5 (6.4) | 3 (6.3) | 2 (6.7) | 1.00 |
| Chronic liver disease | 4 (5.1) | 4 (8.3) | 0 (0) | 0.16 |
| Vital signs | | | | |
| Temperature (°C) | 37.3 [36.7−38.2] | 37.0 [36.5−38.2] | 37.6 [36.9−38.2] | 0.23 |
| Systolic blood pressure (mmHg) | 116 [89−141] | 117 [91−140] | 108 [85−139] | 0.94 |
| Pulse rate (beats/min) | 109 [90−126] | 111 [85−126] | 104 [95−119] | 0.92 |
| Respiratory rate (breaths/min) | 29 [24−32] | 30 [24−30] | 26 [24−34] | 0.94 |
| Laboratory examinations | | | | |
| Alb (g/dL) | 2.9 [2.4−3.3] | 2.9 [2.4−3.3] | 3.0 [2.7−3.3] | 0.38 |
| BUN (mg/dL) | 26 [18−44] | 26 [18−44] | 26 [17−37] | 0.51 |
| Cr (mg/dL) | 1.09 [0.79−1.63] | 1.10 [0.78−1.64] | 1.08 [0.79−1.45] | 0.70 |
| Na (mmol/L) | 138 [134−139] | 136 [134−139] | 138 [135−139] | 0.33 |
| Ht (%) | 38.8 [33.8−42.4] | 37.6 [31.3−41.8] | 39.5 [36.2−42.6] | 0.29 |
| Plt count (× $10^4$/μL) | 19.0 [14.4−25.5] | 18.8 [15.5−25.0] | 19.0 [13.0-26.5] | 0.69 |
| WBC count (× $10^3$/μL) | 10.9 [7.7−16.2] | 11.1 [8.2−16.6] | 10.9 [6.7−15.8] | 0.29 |
| CRP (mg/L) | 154.3 [88.3-294.8] | 152.5 [90.8-299.1] | 187.1 [88.3-283.9] | 0.41 |
| CURB-65 (score) | | | | 0.52 |

Data are presented as medians (interquartile range) or n (%).

Alb, albumin; ALT, alanine aminotransferase; APACHE, acute physiology and chronic health evaluation; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; CURB-65, confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, low blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg), and age ≥ 65 years, Ht, hematocrit; LDH, lactate dehydrogenase; Na, sodium; Plt, platelet; PSI, Pneumonia Severity Index; WBC, white blood cell

[a]β-lactam monotherapy and β-lactam and non-macrolide combination therapy were included.

[b]Diagnosed according to the GOLD definition [37]. Patients who were already diagnosed and treated as having COPD at other hospitals and had emphysema on chest computed tomography were also included.

| | All patients n = 78 | Non-macrolide-containing group[a] n = 48 | Macrolide combination group n = 30 | P value |
|---|---|---|---|---|
| 0 | 3 (3.8) | 1 (2.1) | 2 (6.7) | |
| 1 | 7 (9.0) | 3 (6.3) | 4 (13.3) | |
| 2 | 15 (19.2) | 9 (18.8) | 6 (20.0) | |
| 3 | 24 (30.8) | 14 (29.2) | 10 (33.3) | |
| 4 | 24 (30.8) | 18 (37.5) | 6 (20.0) | |
| 5 | 5 (6.4) | 3 (6.3) | 2 (6.7) | |
| PSI (points) | 143 [117–170] | 150 [122–181] | 131 [98–159] | 0.046 |
| PSI class | | | | 0.16 |
| I | 0 (0) | 0 (0) | 0 (0) | |
| II | 2 (2.6) | 0 (0) | 2 (6.7) | |
| III | 9 (11.5) | 5 (10.4) | 4 (13.3) | |
| IV | 19 (24.4) | 10 (20.8) | 9 (30.0) | |
| V | 48 (61.5) | 33 (68.8) | 15 (50.0) | |
| APACHE II score | 18 [14–22] | 18 [15–23] | 15 [13–21] | 0.14 |
| Bacteremia | 16 (20.5) | 7 (14.6) | 9 (30.0) | 0.38 |
| Steroid use | 28 (35.9) | 16 (33.3) | 12 (40.0) | 0.38 |
| Mechanical ventilation | 60 (76.9) | 38 (79.2) | 22 (73.3) | 0.59 |
| Vasopressor drug use | 50 (64.1) | 30 (62.5) | 20 (66.7) | 0.81 |
| Data are presented as medians (interquartile range) or n (%). | | | | |
| Alb, albumin; ALT, alanine aminotransferase; APACHE, acute physiology and chronic health evaluation; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; CURB-65, confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, low blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg), and age ≥ 65 years, Ht, hematocrit; LDH, lactate dehydrogenase; Na, sodium; Plt, platelet; PSI, Pneumonia Severity Index; WBC, white blood cell | | | | |
| [a]β-lactam monotherapy and β-lactam and non-macrolide combination therapy were included. | | | | |
| [b]Diagnosed according to the GOLD definition [37]. Patients who were already diagnosed and treated as having COPD at other hospitals and had emphysema on chest computed tomography were also included. | | | | |

Initial antibiotic therapy regimen in the non-macrolide-containing therapy and the macrolide combination therapy groups

Table 2 shows the initial antimicrobial agents in the non-macrolide and macrolide combination groups. In the non-macrolide group, the most frequently used antibiotic therapy was sulbactam/ampicillin monotherapy (35.4%), followed by ceftriaxone monotherapy (12.5%). On the other hand, in the macrolide combination group, the most frequently used antibiotic therapy was sulbactam/ampicillin + azithromycin (26.7%), followed by ampicillin + azithromycin (20.0%).

Table 2
Initial antibiotic therapy regimen

| Initial antibiotic regimen | | | |
|---|---|---|---|
| Non-macrolide-containing group | n (%) | Macrolide combination group | n (%) |
| n = 48 | | n = 30 | |
| Penicillin | | Penicillin + Macrolides | |
| Ampicillin | 1 (2.1) | Ampicillin + Azithromycin | 6 (20.0) |
| Sulbactam / ampicillin | 17 (35.4) | Sulbactam / ampicillin + Azithromycin | 8 (26.7) |
| Tazobactam / piperacillin | 3 (6.3) | Tazobactam / piperacillin + Azithromycin | 2 (6.7) |
| Penicillin + Quinolones | | Penicillin G + Azithromycin | 1 (3.3) |
| Sulbactam / ampicillin + Levofloxacin | 2 (4.2) | Penicillin + Macrolides + Others | |
| Sulbactam / ampicillin + Pazufloxacin | 1 (2.1) | Sulbactam / ampicillin + Azithromycin + Levofloxacin | 1 (3.3) |
| Tazobactam / piperacillin + Levofloxacin | 1 (2.1) | Sulbactam / ampicillin + Azithromycin + Meropenem + Vancomycin | 1 (3.3) |
| Cephalosporins | | Cephalosporins + Macrolides | |
| Ceftriaxone | 6 (12.5) | Ceftriaxone + Azithromycin | 5 (16.7) |
| Cephalosporins + Quinolones | | Cephalosporins + Macrolides + Others | |
| Ceftriaxone + Levofloxacin | 2 (4.2) | Ceftriaxone + Azithromycin + Levofloxacin | 2 (6.7) |
| Ceftriaxone + Pazufloxacin | 1 (2.1) | Ceftazidime + Azithromycin + Aztreonam | 1 (3.3) |
| Cefepime + Pazufloxacin | 1 (2.1) | Carbapenems + Macrolides | |
| Cephalosporins + Glycopeptides | | Meropenem + Azithromycin | 2 (6.7) |
| Ceftriaxone + Vancomycin | 2 (4.2) | Carbapenems + Macrolides + Others | |
| Carbapenems | | Meropenem + Azithromycin + Levofloxacin | 1 (3.3) |
| Meropenem | 4 (8.3) | | |
| Carbapenems + Quinolones | | | |
| Meropenem + Pazufloxacin | 2 (4.2) | | |
| Meropenem + Levofloxacin | 1 (2.1) | | |
| Meropenem + Ciprofloxacin | 1 (2.1) | | |
| Carbapenems + Glycopeptides | | | |
| Meropenem + Vancomycin | 1 (2.1) | | |
| Quinolones | | | |
| Levofloxacin | 2 (4.2) | | |

Etiology of pneumonia

The distribution of the causative pathogens in the present study is shown in Table 3. In the non-macrolide group, the most common causative microorganism was *S. pneumoniae* (14.6%), followed by *Haemophilus influenzae* (10.4%), *Moraxella catarrhalis* (10.4%), and methicillin-susceptible *Staphylococcus aureus* (MSSA) (10.4%). However, in the macrolide combination group, the most common pathogen was *S. pneumoniae* (43.3%), followed by MSSA (13.3%).

Table 3
Causative pathogens of pneumonia

| Causative microorganism | Non-macrolide-containing group[a] n = 48 | Macrolide combination group[a] n = 30 |
|---|---|---|
| *Streptococcus pneumoniae* | 7 (14.6) | 13 (43.3) |
| *Haemophilus influenzae* | 5 (10.4) | 0 |
| *Moraxella catarrhalis* | 5 (10.4) | 1 (3.3) |
| *Staphylococcus aureus* | 6 (12.5) | 5 (16.7) |
| Methicillin-susceptible *Staphylococcus aureus* | 5 (10.4) | 4 (13.3) |
| Methicillin-resistant *Staphylococcus aureus* | 1 (2.1) | 1 (3.3) |
| Anaerobes | 2 (4.2) | 1 (3.3) |
| *Streptococcus anginosus* group | 2 (4.2) | 0 |
| *Streptococcus* species | 1 (2.1) | 2 (6.7) |
| *Pseudomonas aeruginosa* | 1 (2.1) | 2 (6.7) |
| *Bacillus cereus* | 1 (2.1) | 0 |
| *Pasteurella multocida* | 1 (2.1) | 0 |
| *Proteus mirabilis* | 1 (2.1) | 0 |
| *Chlamydophila pneumoniae* | 1 (2.1) | 1 (3.3) |
| *Mycoplasma pneumoniae* | 1 (2.1) | 0 |
| Influenza virus | 1 (2.1) | 1 (3.3) |
| *Escherichia coli* | 0 | 1 (3.3) |
| *Acinetobacter baumannii* | 0 | 1 (3.3) |
| Multiple etiologies | 7 (14.6) | 3 (10.0) |
| Unknown | 21 (43.8) | 5 (16.7) |

[a]There were 7 and 3 patients with multiple etiologies in the non-macrolide therapy group and the macrolide combination group, respectively; therefore, the sum of the infection rates is over 100%.

Outcome after adjustment by propensity score analysis

Table 4 shows the standardized mean differences of the six covariates before and after adjustment by IPTW analysis. The standardized mean differences were less than 0.1 for all covariates. After adjusting by IPTW analysis, the macrolide combination group had significantly decreased 30-day mortality (odds ratio 0.29, 95% confidence interval 0.09−0.96, $P = 0.04$) and 14-day mortality (odds ratio 0.19, 95% confidence interval 0.04−0.92, $P = 0.04$), but ICU mortality was not significantly decreased (odds ratio 0.34, 95% confidence interval 0.08−1.36, $P = 0.13$) (Table 5).

Table 4
Standardized mean differences before and after propensity score analysis

| | Standardized mean difference | |
| --- | --- | --- |
| Covariate | Before IPTW | After IPTW |
| Age | 0.53 | 0.05 |
| Sex | 0.16 | 0.02 |
| C-reactive protein | 0.25 | 0.02 |
| Albumin | 0.19 | 0.009 |
| Pneumonia Severity Index | 0.50 | 0.08 |
| APACHE II score | 0.06 | 0.07 |
| APACHE, acute physiology and chronic health evaluation; IPTW, inverse probability of treatment weighting | | |

Table 5
30-day mortality, 14-day mortality, and ICU mortality with macrolide combination therapy for severe community-acquired pneumonia

| | 30-day mortality | | | | 14-day mortality | | | | ICU mortality | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Before IPTW analysis | | After IPTW analysis | | Before IPTW analysis | | After IPTW analysis | | Before IPTW analysis | | After IPTW analysis | |
| | OR (95% CI) | $P$ value | OR (95% CI) | $P$ value | OR (95% CI) | $P$ value | OR (95% CI) | $P$ value | OR (95% CI) | $P$ value | OR (95% CI) | $P$ value |
| Macrolide combination therapy | 0.26 (0.08–0.74) | 0.02 | 0.29 (0.09–0.96) | 0.04 | 0.16 (0.02–0.62) | 0.02 | 0.19 (0.04–0.92) | 0.04 | 0.30 (0.06–1.04) | 0.08 | 0.34 (0.08–1.36) | 0.13 |
| CI, confidence interval; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; OR, odds ratio | | | | | | | | | | | | |

# Discussion

The present study showed that macrolide combination therapy significantly decreased 30-day and 14-day mortality, but not ICU mortality compared with β-lactam monotherapy or β-lactam and non-macrolide-containing combination therapy. After adjusting by IPTW analysis, macrolide combination therapy also significantly improved 30-day and 14-day mortality, though ICU mortality was not significantly decreased.

Many previous studies reported that macrolide combination therapy improved prognosis compared with non-macrolide-containing regimens [8–13]. However, all of the studies were observational cohort studies including prospective and retrospective parts, and there were no RCTs. In addition, there have been few studies that used propensity scores to reduce various biases [11]. Thus, whether macrolide combination therapy truly reduces mortality in SCAP patients hospitalized in the ICU is controversial, although a previous meta-analysis study stated that "this meta-analysis supported the use of macrolides as a first-line combination treatment in critically ill patients with severe CAP" [25]. In the present study, IPTW analysis was used to reduce as much as possible some previously known biases related to prognostic factors. Therefore, the present study's results confirm those of the previous studies.

Regarding ICU mortality, the present study did not show the usefulness of macrolide combination therapy. The reason was thought to be due to the fact that 5 patients died in the medical ward within 30 days of admission in the non-macrolide combination group. These patients were transferred to a medical ward from the ICU due to a do not attempt resuscitation order.

Indeed, if all 5 patients were included as ICU mortality cases, macrolide combination therapy significantly reduced ICU mortality compared with non-macrolide-containing therapy after IPTW analysis (odds ratio 0.22, 95% confidence interval 0.06−0.85, $P$ = 0.03) (data not shown).

In the guidelines for CAP in the United States and Europe [1, 7], combination antibiotic therapy including β-lactam and macrolides or β-lactam and quinolones was recommended for SCAP patients hospitalized in the ICU. Based on these guidelines and the results of the present study, macrolide combination therapy appears to be more suitable for SCAP patients than β-lactam monotherapy, although Japanese CAP guidelines state that β-lactam monotherapy is a valid antibiotic regimen for SCAP patients hospitalized in the ICU [26].

There is another question related to which antibiotic regimen including β-lactam and macrolides or quinolones is better for treatment of SCAP patients. Some studies showed that guideline-concordant therapy was important to improve the prognosis of SCAP, but not specific treatment regimens [10, 27, 28]. In the present study, mortality was not compared between β-lactam and macrolide combination therapy and β-lactam and quinolone combination therapy because only a few patients were treated using β-lactam and quinolone combination therapy (n = 12). Therefore, whether macrolide combination therapy significantly reduces mortality compared with β-lactam and quinolone combination therapy remains unknown.

However, there are some reasons that macrolide combination therapy may be preferred to quinolone combination therapy. First, Martin-Loeches et al reported that macrolide combination therapy significantly reduced 30-day ICU mortality compared to β-lactam and quinolone combination therapy in patients treated using mechanical ventilatory support (26.1% vs. 46.3%, $P$ = 0.04) in a prospective cohort study. They also showed that macrolide combination therapy significantly improved outcomes in severe sepsis and septic shock patients [12]. On the other hand, Mortensen et al showed that initial empiric antibiotic therapy with β-lactam and fluoroquinolone combination therapy was associated with significantly increased 30-day mortality for SCAP patients compared with other guideline-concordant therapy using a propensity score analysis in a retrospective cohort study [29]. Second, macrolides have some immunomodulatory effects [30, 31]. Anderson et al reported that macrolides significantly decreased pneumolysin production by *S. pneumoniae*, but fluoroquinolones and ceftriaxone did not [32]. In addition, a meta-analysis of 28 RCTs showed that empiric atypical coverage did not significantly improve the prognosis in hospitalized CAP patients [33], and macrolides and β-lactam antibiotics have no synergistic effects [34, 35]. Therefore, we think that immunomodulatory effects of macrolides have an important role in improving the prognosis, as stated above. Indeed, high levels of both pro- and anti-inflammatory cytokines have been reported to cause a poor prognosis for SCAP patients, even in patients who received appropriate antibiotic therapy [36].

The present study has some limitations. First, it was a single-center study with a relatively small number of patients, and whether the present results can be generalized to other areas and other countries is unknown. Second, this study was also an observational cohort study like many previous studies, and a future RCT is needed to confirm these results.

Regardless of the above limitations, the present study has some strengths. It was the first study of macrolide combination therapy in an Asian country. All previous studies that showed the efficacy of macrolide combination therapy were conducted in the United States and Europe. Therefore, the results of the present study are thought to be significant because they show the usefulness of macrolide combination therapy in other countries. Furthermore, the present study reduced some biases as much as possible using propensity score analysis, although it was not an RCT.

## Conclusions

In conclusion, macrolide combination therapy is useful for reducing mortality in SCAP patients hospitalized in the ICU compared with β-lactam monotherapy or non-macrolide-containing β-lactam combination therapy. To improve the prognosis of SCAP patients, among the guideline-concordant therapies, macrolide combination therapy may contribute to better survival.

## Abbreviations

CAP

community-acquired pneumonia; CURB-65:confusion, urea > 7 mmol/L, respiratory rate ≥ 30 breaths per minute, low blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg), and age ≥ 65 years; HCAP:healthcare-associated pneumonia; ICU:intensive care unit; IPTW:inverse probability of treatment weighting; MSSA:methicillin-susceptible *Staphylococcus aureus*; PS:propensity score; PSI:Pneumonia Severity Index; RCT:randomized, controlled trial; SCAP:severe community-acquired pneumonia

## Declarations

### Ethics approval and consent to participate

This study was approved by the institutional review board of Kurashiki Central Hospital (approval number 3398). All patients gave their informed consent to participate in this study. The study was performed in accordance with the ethical standards laid

down in the 1964 Declaration of Helsinki and its later amendments.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

All authors have no conflicts of interest to declare.

### Authors' contributions

AI served as the principal author, had full access to all data in the study, and takes responsibility for the integrity and accuracy of the data and data analysis. AI, TI, HT, YN, FT, AY, YW, HI, and TO contributed to the study conception and design and to the acquisition of data. AI, TI, and HT contributed to the analysis and interpretation of data. AI, TI, HT, YN, FT, AY, YW, HI, and TO contributed to the drafting and revision of the manuscript and approved the final version to be submitted for consideration for publication.

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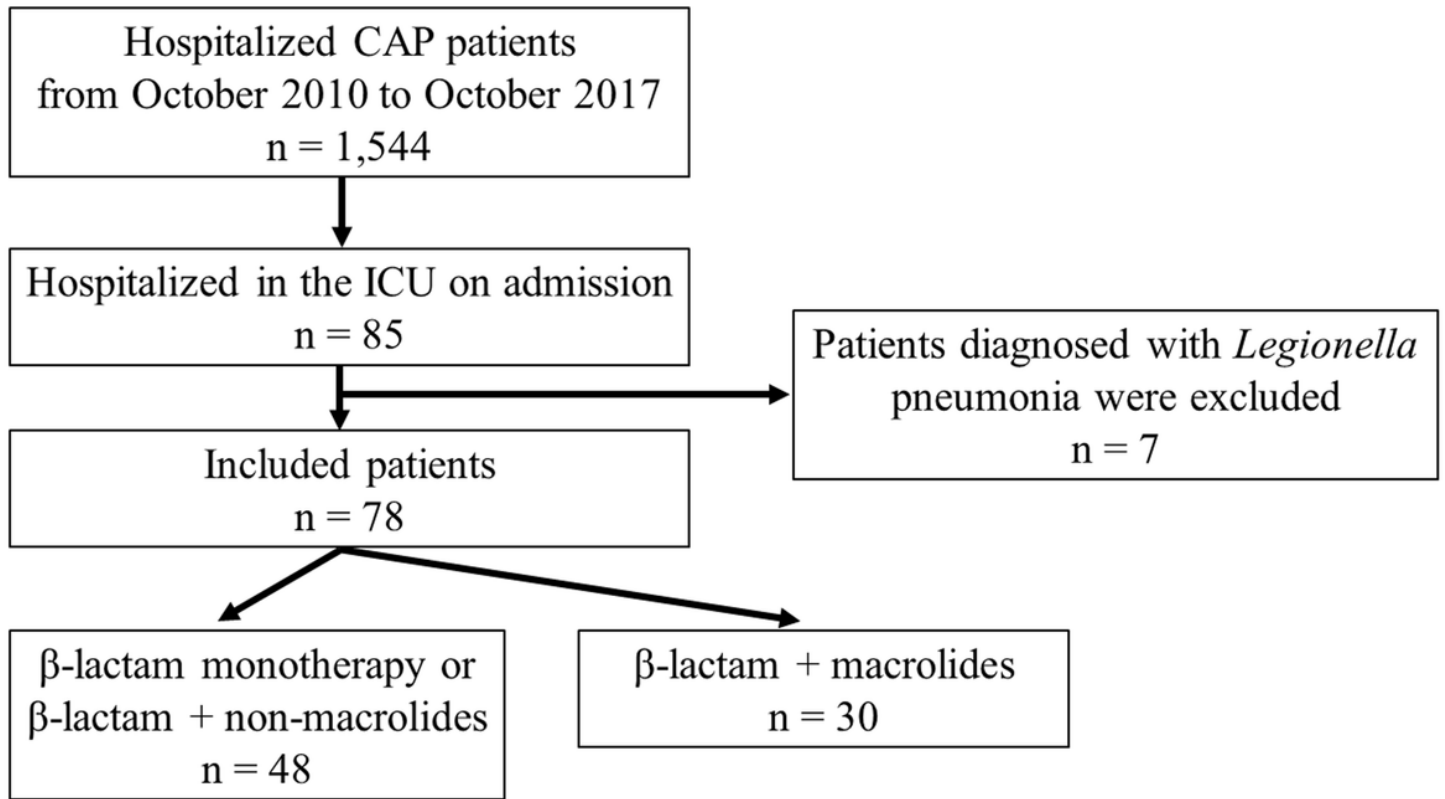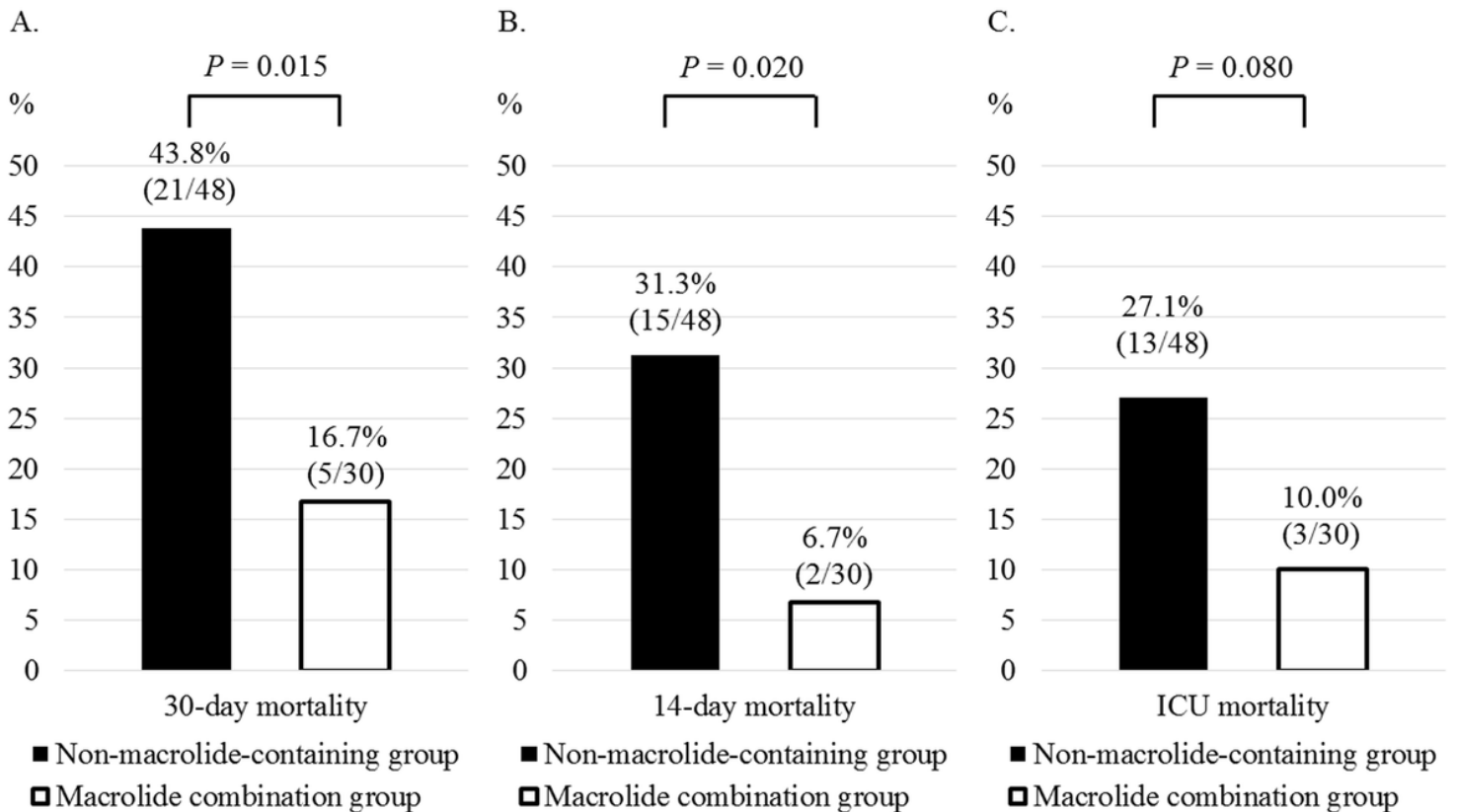
## Figures



**Figure 1**

Study flowchart

**Figure 2**

30-day mortality, 14-day mortality, and ICU mortality in the non-macrolide-containing group and the macrolide combination group A. 30-day mortality, B. 14-day mortality, C. ICU mortality The non-macrolide-containing group includes β-lactam monotherapy and β-lactam and non-macrolide combination therapy. ICU, intensive care unit