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Original Article

Azithromycin plus β-lactam versus levofloxacin plus β-lactam for severe community-acquired pneumonia: A retrospective nationwide database analysis

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ABSTRACT

Previous studies showed potential benefits of macrolide combined with β-lactam for severe community-acquired pneumonia (CAP). However, it remains inconclusive whether macrolide plus β-lactam is superior to respiratory fluoroquinolone plus β-lactam for patients with severe CAP. Using a nationwide inpatient database in Japan, we performed propensity score matching and inverse probability of treatment weighting (IPTW) to compare 28-day mortality and in-hospital mortality between azithromycin plus β-lactam and levofloxacin plus β-lactam for severe CAP patients admitted to hospital between July 2010 and March 2015. We identified 1,999 patients with severe pneumonia who received azithromycin plus β-lactam (n = 840) or levofloxacin plus β-lactam (n = 1,159) within 2 days after admission. Five-hundred sixty propensity score-matched pairs showed no significant differences between azithromycin plus β-lactam and levofloxacin plus β-lactam in 28-day mortality and in-hospital mortality (19.3% vs. 20.7%, p = 0.601 and 24.8% vs. 26.8%, p = 0.495, respectively). IPTW analysis also showed no significant differences between azithromycin plus β-lactam and levofloxacin plus β-lactam in 28-day mortality (risk difference, −3.5% [95% confidence interval, −8.8% to 1.7%] and in-hospital mortality (risk difference, −3.6%; 95% confidence interval, −9.4% to 2.1%). In conclusion, there were no significant differences in 28-day mortality and in-hospital mortality between azithromycin plus β-lactam and levofloxacin plus β-lactam for severe CAP patients.

1. Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of sepsis [1,2]. Approximately 40–80% of critically ill patients with CAP require mechanical ventilation, up to 50% of patients progress to septic shock [3], and the reported mortality of severe CAP is 11%–56% [3,4].

Several studies showed that combinations of antibiotics can reduce mortality in patients with severe CAP [5,6] and recent guidelines recommend macrolide or respiratory fluoroquinolone plus β-lactam for severe CAP [7–9]. A subgroup analysis in one systematic review and meta-analysis showed that macrolide plus β-lactam had a tendency to reduce mortality (risk ratio, 0.83 [95% confidence interval (CI), 0.67–1.03]) in critically ill patients with severe CAP compared with fluoroquinolone plus β-lactam [4].

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However, the fluoroquinolones in the meta-analysis included non-respiratory fluoroquinolones that do not cover *Streptococcus pneumoniae* [4].

Few studies have compared macrolide plus β-lactam and respiratory fluoroquinolone plus β-lactam for patients with severe CAP. A retrospective single-center study on 210 patients with severe CAP investigated the difference between azithromycin or erythromycin plus β-lactam and respiratory fluoroquinolone (moxifloxacin or levofloxacin) plus β-lactam [10]. Although the study did not show statistical significance, azithromycin or erythromycin plus β-lactam was associated with approximately 8% higher mortality in severe CAP patients compared with moxifloxacin or levofloxacin plus β-lactam (24.5% vs. 16.3%, $p = 0.17$). Thus, it remains inconclusive whether azithromycin plus β-lactam has beneficial effects compared with levofloxacin plus β-lactam in patients with severe CAP.

The aim of the present study was to compare 28-day mortality and in-hospital mortality between azithromycin plus β-lactam and levofloxacin plus β-lactam for patients with severe CAP using a Japanese national inpatient database.

2. Material and methods

2.1. Data source

Data for the study were abstracted from the Japanese Diagnosis Procedure Combination (DPC) database, which includes data for approximately 7 million inpatients per year from more than 1,000 acute-care hospitals in Japan, representing approximately 50% of all discharges from acute-care hospitals in Japan.

The database contains the following data: hospital identification number, age, sex, primary diagnosis, comorbidities at admission, post-admission complications during hospitalization, dates of hospital admission and discharge, and discharge status (dead or alive). All primary diagnoses, comorbidities at admission, and post-admission complications during hospitalization are encoded with International Classification of Diseases, 10th revision (ICD-10) codes and text written in Japanese language. The database also contains dates of procedures and drug prescriptions [11–13].

2.2. Patient data

We identified patients with severe pneumonia hospitalized between July 2010 and March 2015. We included patients diagnosed with severe pneumonia and sepsis who received β-lactam within 2 days after admission, and also received azithromycin or levofloxacin. Sepsis was defined as patients with any bacterial or fungal infection at admission based on the Angus criteria (Supplementary Table S1) [14]. The definition of sepsis has been validated in the DPC database (specificity and positive predictive value of approximately 80%) [15]. Pneumonia was identified by ICD-10 codes J13–J18 as the primary diagnosis or comorbidities at admission. Severe pneumonia was defined as patients diagnosed with pneumonia who required vasopressors and/or mechanical ventilation within 2 days after admission, according to the Infectious Diseases Society of America/American Thoracic Society Consensus guidelines [8]. The exclusion criteria were: 1) age <18 years; 2) discharge within 2 days of admission; 3) pregnancy; 4) malignancy; 5) autoimmune diseases; 6) human immunodeficiency virus infection or acquired immunodeficiency syndrome; 7) intravenous ciprofloxacin use within 2 days of admission; 8) intravenous erythromycin use within 2 days of admission; and 9) oral garenoxacin use within 2 days of admission.

2.3. Study variables

The exposure of interest was whether patients received intravenous azithromycin plus β-lactam (azithromycin group) or intravenous levofloxacin plus β-lactam (levofloxacin group) within 2 days of admission.

Other variables included age, sex, hospital type (academic or nonacademic), hospital volume of patients with severe pneumonia, comorbidities, Japan coma scale (JCS), and A-DROP (age, dehydration, respiration, orientation, blood pressure) system. Hospital volume of patients with severe pneumonia was defined as the average annual number of patients with severe pneumonia in each hospital, according to the Infectious Diseases Society of America/American Thoracic Society Consensus guidelines [8]. JCS scores were recorded in all patients to assess the level of consciousness on admission, and are well correlated with the Glasgow Coma Scale [16]. The JCS scores were categorized into four groups: 0 (alert), 1–3 (delirium), 10–30 (somnolence), and 100–300 (coma) [17,18]. We used the A-DROP system to evaluate the severity of CAP on admission, according to the Japanese Respiratory Society [9]. This scoring system is similar to the CURB-65 system of the British Thoracic Society [19]. The A-DROP severity scores in patients with CAP are also a good predictor for mortality and have been validated in the DPC database [20]. The A-DROP severity scores were categorized into four groups according to the Japanese Respiratory Society [9]: 0, patients with mild condition who can be treated as outpatients (mild group); 1–2, patients with moderate condition who may be admitted to hospital (moderate group); 3, patients with severe condition who should be admitted to hospital (severe group); and 4–5, patients with extremely severe condition who should take into intensive care (extremely severe group) [9,21]. The following procedures within 2 days of admission were evaluated: use of mechanical ventilation, intermittent and continuous renal replacement therapy, polymyxin B hemoperfusion, bacterial culture collection, bronchoscopy, vasopressors including noradrenalin and dopamine, intravenous hydrocortisone, intravenous dexamethasone, intravenous prednisolone, intravenous methyl prednisolone, immunoglobulin, heparin, low-molecular-weight heparin, danaparoid, recombinant human soluble thrombomodulin, antithrombin, sivelestat sodium, enteral nutrition, total parenteral nutrition, intravenous amino-acid transfusion, and intravenous fat emulsion, primary use of antibiotics (penicillin, ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, first-generation cephalosporin, second-generation cephalosporin, third-generation cephalosporin with or without effect for *Pseudomonas aeruginosa*, fourth-generation cephalosporin, carbapenem, aminoglycoside, tetracycline, clindamycin, anti-methicillin-resistant *Staphylococcus aureus* drugs, antifungal drugs), and transfusions (red cells, platelet concentrates, fresh-frozen plasma).

2.4. Outcomes

The outcomes were 28-day mortality and in-hospital mortality.

2.5. Statistical analysis

Descriptive statistics were evaluated before and after propensity score matching and after inverse probability of treatment weighting (IPTW). Continuous variables were presented as means with standard deviations. Categorical variables were presented as numbers with percentages.

One-to-one propensity score matching was performed to adjust for differences in baseline characteristics and severities of conditions on admission between the azithromycin group and the

levofloxacin group. The probability that a patient received azithromycin plus β-lactam was modeled for confounders in the following characteristics: age, sex, hospital type (academic or nonacademic), hospital volume, consciousness level, A-DROP, comorbidities at admission, use of mechanical ventilation, intermittent and continuous renal replacement therapy, polymyxin B hemoperfusion, bacterial culture collection, bronchoscopy, vasopressors including noradrenalin and dopamine, hydrocortisone, intravenous hydrocortisone, intravenous dexamethasone, intravenous prednisolone, intravenous methyl prednisolone, immunoglobulin, heparin, low-molecular-weight heparin, danaparoid, recombinant human soluble thrombomodulin, antithrombin, sivelestat sodium, enteral nutrition, total parenteral nutrition, intravenous amino-acid transfusion, and intravenous fat emulsion, primary use of antibiotics, and transfusion. Using standardized mean differences (SMDs), we assessed differences in patient background characteristics between the azithromycin group and the levofloxacin group before and after propensity score matching and after IPTW [22]. Absolute SMDs of less than 0.1 were considered negligible imbalances in baseline characteristics between the groups [23]. Fisher's exact test was used to compare 28-day mortality and in-hospital mortality between the groups. We also estimated the treatment effect by IPTW of the propensity scores. We calculated risk differences and their 95% CIs between the unmatched, propensity score-matched, and IPTW analysis groups [24]. A p-value of less than 0.05 was considered statistically significant. Propensity score matching was performed using the 'matching' package in statistical software R version 3.1.3 (The R Foundation, Vienna, Austria). IPTW analyses were performed using the 'survey' package in statistical software R version 3.1.3. All other analyses were performed using IBM SPSS software version 25 (IBM SPSS, Armonk, NY).

3. Results

After application of the inclusion and exclusion criteria, 1,999 patients with severe pneumonia were identified in the DPC database between July 2010 and March 2015. Of these patients, 840 patients were assigned to the azithromycin group and 1,159 patients were assigned to the levofloxacin group. After one-to-one propensity score matching, 560 pairs were created (Fig. 1).

Table 1 shows the baseline characteristics in the unmatched and propensity score-matched groups. After propensity score matching, the patient background characteristics were well-balanced between the groups.

Table 2 shows the 28-day mortality and in-hospital mortality in the azithromycin group and the levofloxacin group. Before propensity score matching, 28-day mortality and in-hospital mortality for the azithromycin group and the levofloxacin group were 16.1% vs. 26.1% ($p < 0.001$) and 21.0% vs. 33.6% ($p < 0.001$), respectively.

After propensity score matching, 28-day mortality and in-hospital mortality for the azithromycin group and the levofloxacin group did not differ significantly (19.3% vs. 20.7%, $p = 0.601$ and 24.8% vs. 26.8%, $p = 0.495$, respectively). In the IPTW analysis, 28-day mortality and in-hospital mortality for the azithromycin group and the levofloxacin group did not differ significantly (20.2% vs. 23.9%, $p = 0.180$ and 26.1% vs. 30.3%, $p = 0.217$, respectively).

Table 3 shows the risk differences for 28-mortality and in-hospital mortality in the azithromycin group and the levofloxacin group. Before propensity score matching, the azithromycin group was associated with lower 28-day mortality and in-hospital mortality compared with the levofloxacin group (risk difference, −5.8% [95% CI, −8.9% to −2.7%] and −7.3% [95% CI, −10.7% to −3.9%], respectively). After propensity score matching, there were no significant differences in 28-day mortality and in-hospital mortality between the azithromycin group and the levofloxacin group (risk difference, −0.7% [95% CI, −4.7% to 3.1%] and −1.0% [95% CI, −5.4 to 3.4%], respectively). In the IPTW analysis, there were also no significant differences in 28-day mortality and in-hospital mortality between the azithromycin group and the levofloxacin group (risk difference, −3.5% [95% CI, −8.8 to 1.7%] and −3.6% [95% CI, −9.4 to 2.1%]) (Table 3 and Supplementary Table A2).

4. Discussion

In this retrospective study using a nationwide inpatient database, there were no significant differences in 28-day mortality and in-hospital mortality between azithromycin plus β-lactam and levofloxacin plus β-lactam for severe CAP patients.

Several possible reasons are considered for our results that 28-day mortality and in-hospital mortality were not significantly different between the groups. First, although azithromycin has beneficial immunomodulatory effect for improving pneumonia, levofloxacin may also have the same effect for patients with severe CAP. Macrolides may reduce inflammatory cytokines like tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, and

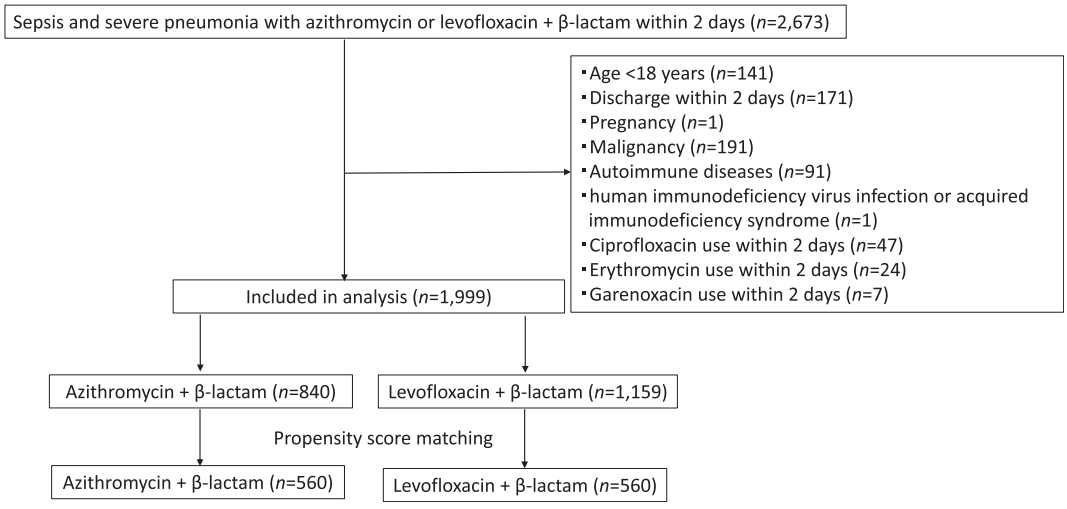

Fig. 1. Patient selection chart.

Table 1
Patient baseline characteristics in the unmatched and propensity score-matched groups.

	Unmatched groups		SMD	Propensity score-matched groups		SMD
	Azithromycin plus β-lactam	Levofloxacin plus β-lactam		Azithromycin plus β-lactam	Levofloxacin plus β-lactam	
Variables	*n* = 840	*n* = 1,159		*n* = 560	*n* = 560	
Age (years), mean (SD)	72.6 (15.0)	71.8 (13.8)	0.06	72.7 (14.1)	72.4 (14.5)	0.02
Sex (female), *n* (%)	272 (32.4)	341 (29.4)	0.06	177 (31.6)	182 (32.5)	0.02
Hospital type (academic), *n* (%)	175 (20.8)	311 (26.8)	0.14	159 (28.4)	135 (24.1)	0.098
Hospital volume, cases/year, mean (SD)	119 (67.3)	111 (54.8)	0.13	115.5 (62.6)	112.4 (56.0)	0.05
Comorbidities, *n* (%)						
Myocardial infarction	33 (3.9)	24 (2.1)	0.11	18 (3.2)	16 (2.9)	0.02
Congestive heart failure	266 (31.7)	311 (26.8)	0.11	157 (28.0)	174 (31.1)	0.07
Peripheral vascular disease	21 (2.5)	16 (1.4)	0.08	13 (2.3)	12 (2.1)	0.01
Cerebrovascular disease	34 (4.0)	80 (6.9)	0.13	28 (5.0)	31 (5.5)	0.02
Dementia	16 (1.9)	28 (2.4)	0.04	15 (2.7)	13 (2.3)	0.02
Chronic pulmonary disease	198 (23.6)	193 (16.7)	0.17	119 (21.2)	113 (20.2)	0.03
Peptic ulcer	39 (4.6)	50 (4.3)	0.02	28 (5.0)	28 (5.0)	<0.001
Mild liver disease	16 (1.9)	51 (4.4)	0.14	13 (2.3)	11 (2.0)	0.03
Severe liver disease	3 (0.4)	2 (0.2)	0.04	1 (0.2)	2 (0.4)	0.035
Hemiplegia or paraplegia	2 (0.2)	2 (0.2)	0.01	1 (0.2)	1 (0.2)	<0.001
Diabetes without chronic complications	129 (15.4)	183 (15.8)	0.01	79 (14.1)	98 (17.5)	0.09
Diabetes with chronic complications	48 (5.7)	60 (5.2)	0.02	32 (5.7)	26 (4.6)	0.05
Renal disease	81 (9.6)	80 (6.9)	0.10	51 (9.1)	42 (7.5)	0.06
Consciousness levels, *n* (%)						
Alert	571 (68.0)	690 (59.5)	0.18	348 (62.1)	359 (64.1)	0.04
Delirium	161 (19.2)	242 (20.9)	0.04	119 (21.2)	112 (20.0)	0.03
Somnolence	54 (6.4)	91 (7.9)	0.06	45 (8.0)	42 (7.5)	0.02
Coma	40 (4.8)	112 (9.7)	0.19	37 (6.6)	37 (6.6)	<0.001
A-DROP categories, *n* (%)						
Mild	30 (3.6)	23 (2.0)	0.10	20 (3.6)	17 (3.0)	0.03
Moderate	256 (30.5)	239 (20.6)	0.23	139 (24.8)	143 (25.5)	0.02
Severe	133 (15.8)	186 (16.0)	0.01	87 (15.5)	87 (15.5)	<0.001
Extremely severe	152 (18.1)	267 (23.0)	0.12	113 (20.2)	123 (22.0)	0.04
Missing data	299 (35.6)	467 (40.3)	0.10	221 (39.5)	207 (37.0)	0.05
Interventions, *n* (%)						
Mechanical ventilation	645 (76.8)	983 (84.8)	0.21	448 (80.0)	443 (79.1)	0.02
Intermittent renal replacement therapy	30 (3.6)	98 (8.5)	0.21	27 (4.8)	34 (6.1)	0.02
Continuous renal replacement therapy	39 (4.6)	24 (2.1)	0.14	22 (3.9)	17 (3.0)	0.05
Polymyxin B hemoperfusion	13 (1.5)	44 (3.8)	0.14	13 (2.3)	17 (3.0)	0.05
Bacterial culture taken	769 (91.5)	1088 (93.9)	0.09	521 (93.0)	511 (91.2)	0.07
Bronchoscopy	26 (3.1)	58 (5.0)	0.10	21 (3.8)	22 (3.9)	0.01
Catecholamines, *n* (%)						
Dopamine	199 (23.7)	314 (27.1)	0.08	135 (24.1)	129 (23.0)	0.03
Noradrenaline	197 (23.5)	428 (36.9)	0.30	166 (29.6)	161 (28.7)	0.02
Nutrition, *n* (%)						
enteral nutrition	117 (13.9)	205 (17.7)	0.10	87 (15.5)	79 (14.1)	0.04
total parenteral nutrition	32 (3.8)	101 (8.7)	0.20	28 (5.0)	27 (4.8)	0.01
intravenous amino-acid transfusion	138 (16.4)	254 (21.9)	0.14	107 (19.1)	112 (20.0)	0.02
intravenous fat emulsion	8 (1.0)	16 (1.4)	0.04	7 (1.2)	5 (0.9)	0.04
Red cell transfusion, *n* (%)	43 (5.1)	75 (6.5)	0.06	31 (5.5)	36 (6.4)	0.04
Platelets transfusion, *n* (%)	10 (1.2)	28 (2.4)	0.09	8 (1.4)	12 (2.1)	0.05
Fresh-frozen plasma transfusion, *n* (%)	9 (1.1)	24 (2.1)	0.08	7 (1.2)	10 (1.8)	0.04
Antithrombin, *n* (%)	22 (2.6)	112 (9.7)	0.30	21 (3.8)	26 (4.6)	0.05
Recombinant human soluble thrombomodulin, *n* (%)	25 (3.0)	123 (10.6)	0.31	23 (4.1)	23 (4.1)	<0.001
Immunoglobulin, *n* (%)	51 (6.1)	210 (18.1)	0.38	47 (8.4)	56 (10.0)	0.06
Heparin, *n* (%)	437 (52.0)	695 (60.0)	0.16	310 (55.4)	312 (55.7)	0.007
Danaparoid, *n* (%)	10 (1.2)	8 (0.7)	0.05	7 (1.2)	5 (0.9)	0.04
Sivelestat sodium, *n* (%)	46 (5.5)	261 (22.5)	0.51	46 (8.2)	43 (7.7)	0.02
Low-molecular-weight heparin, *n* (%)	7 (0.8)	12 (1.0)	0.02	4 (0.7)	1 (0.2)	0.08
Steroid, *n* (%)						
Intravenous dexamethasone	7 (0.8)	14 (1.2)	0.04	5 (0.9)	4 (0.7)	0.02
Intravenous prednisolone	27 (3.2)	73 (6.3)	0.15	24 (4.3)	21 (3.8)	0.03
Intravenous methyl prednisolone	135 (16.1)	293 (25.3)	0.23	102 (18.2)	101 (18.0)	0.01
Intravenous hydrocortisone	76 (9.0)	178 (15.4)	0.19	65 (11.6)	67 (12.0)	0.01
Initial antibiotics, *n* (%)						
Penicillin	3 (0.4)	4 (0.3)	0.002	2 (0.4)	2 (0.4)	<0.001
Ampicillin	9 (1.1)	2 (0.2)	0.12	4 (0.7)	4 (0.7)	<0.001

(*continued on next page*)

Table 1 (*continued*)

	Unmatched groups		SMD	Propensity score-matched groups		SMD
	Azithromycin plus β-lactam	Levofloxacin plus β-lactam		Azithromycin plus β-lactam	Levofloxacin plus β-lactam	
Ampicillin/sulbactam	209 (24.9)	199 (17.2)	0.19	138 (24.6)	148 (26.4)	0.01
Piperacillin	8 (1.0)	8 (0.7)	0.03	5 (0.9)	4 (0.7)	0.02
Piperacillin/tazobactam	181 (21.5)	243 (21.0)	0.01	146 (26.1)	148 (26.4)	0.01
First-generation cephalosporin	4 (0.5)	2 (0.2)	0.05	2 (0.4)	2 (0.4)	<0.001
Second-generation cephalosporin	7 (0.8)	5 (0.4)	0.05	4 (0.7)	4 (0.7)	<0.001
Third-generation cephalosporin without effect for *Pseudomonas aeruginosa*	338 (40.2)	190 (16.4)	0.55	159 (28.4)	156 (27.9)	0.01
Third-generation cephalosporin with effect for *Pseudomonas aeruginosa*	10 (1.2)	5 (0.4)	0.09	3 (0.5)	5 (0.9)	0.04
Fourth-generation cephalosporin	26 (3.1)	27 (2.3)	0.05	17 (3.0)	17 (3.0)	<0.001
Carbapenem	193 (23.0)	646 (55.7)	0.71	180 (32.1)	178 (31.8)	0.01
Aminoglycoside	8 (1.0)	6 (0.5)	0.05	5 (0.9)	4 (0.7)	0.02
Tetracycline	10 (1.2)	26 (2.2)	0.08	7 (1.2)	9 (1.6)	0.03
Clindamycin	11 (1.3)	18 (1.6)	0.02	7 (1.2)	9 (1.6)	0.03
Anti-MRSA drug	39 (4.6)	81 (7.0)	0.10	31 (5.5)	34 (6.1)	0.06
Antifungal drug	1 (0.1)	9 (0.8)	0.10	1 (0.2)	1 (0.2)	<0.001

Abbreviations: SMD, standardized mean difference; SD, standard deviation; A-DROP, severity score consisting of age, dehydration, respiration, orientation, and blood pressure; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2
Rates for 28-day mortality and in-hospital mortality in the unmatched, propensity score-matched, and IPTW analysis groups.

Outcome, *n* (%)	Unmatched groups			Propensity score-matched groups			IPTW analysis groups		
	Azithromycin plus β-lactam	levofloxacin plus β-lactam	*p*	Azithromycin plus β-lactam	levofloxacin plus β-lactam	*p*	Azithromycin plus β-lactam	levofloxacin plus β-lactam	*p*
	n = 840	*n* = 1,159		*n* = 560	*n* = 560		*n* = 2,073	*n* = 2,002	
28-day mortality	135 (16.1)	302 (26.1)	<0.001	108 (19.3)	116 (20.7)	0.601	409 (19.8)	478 (23.9)	0.180
In-hospital mortality	176 (21.0)	389 (33.6)	<0.001	139 (24.8)	150 (26.8)	0.495	552 (26.6)	605 (30.2)	0.217

Abbreviation: IPTW, inverse probability of treatment weighting.

interferon-γ [25,26]. On the other hand, levofloxacin also has an anti-inflammatory effect and it may be similar effect for inhibition of inflammatory cytokines compared with azithromycin [27]. Second, compared with levofloxacin plus β-lactam, similar effects for azithromycin plus β-lactam have been reported for: 1) atypical pathogens, 2) double coverage of pneumococcus resistance as the leading pathogen of pneumonia, and 3) two different mechanisms of antibiotic action [28–31]. Therefore, these similar effects may explain our results.

The differing susceptibilities of pneumonia pathogens can also explain our results. In Japan, approximately 80% of *S. pneumoniae* strains, as the leading CAP pathogens, are resistant to azithromycin, while 98% of *S. pneumoniae* strains are susceptible to levofloxacin [32]. Although macrolide showed additional anti-inflammatory effects regardless of azithromycin resistance [33] and β-lactam can cover pathogens with azithromycin resistance, the benefits of azithromycin may be decreased or abolished by differences in susceptibilities and our results may not be generalizable to other countries because of differences in susceptibility.

We acknowledge that the present study has several limitations. First, the DPC database lacks clinical data such as results of cultures. The names of specific organisms such as *Pseudomonas aeruginosa* or *Legionella pneumophilia* and their susceptibilities are not known. However, the proportion of CAP due to *P. aeruginosa* was very low in Japan [34] and our results showed that the proportion of patients who received antipseudomonal β-lactam antibiotics were well-balanced between the groups. On the other hand, *Legionella pneumophilia* has been reported to be approximately 14% of the pathogens in patients with severe CAP in Japan [34,35]. However, one cohort study showed that there was no difference in mortality between azithromycin and levofloxacin in pneumonia patients due to *Legionella pneumophilia* [36]. We therefore believe that these organisms had only small influence on our results. Second, the antibiotic susceptibilities of organisms that cause pneumonia in Japan may be different from those in other countries [37,38]. The generalizability of the present findings may thus be limited. Third, in our study, the definition of severe pneumonia was based on major criteria according to the Infectious Diseases Society of America/American Thoracic Society Consensus guidelines. We could not include severe pneumonia based on minor criteria according to the same guidelines [8] because the DPC database lacks clinical data such as results of vital signs and laboratory data. Forth, we did not investigate the amounts and durations of antibiotic use. Fifth, data for the A-DROP system as a severity of the pneumonia included missing data, which may have biased the results. Sixth, the DPC database lacks previous history of hospitalization, colonization of antimicrobial resistance organisms, and antimicrobial treatment, which may have influenced the antibiotics selection.

Table 3
Risk differences for 28-day mortality and in-hospital mortality in the unmatched, propensity score-matched, and IPTW analysis groups.

	Unmatched groups	*p*	Propensity score-matched groups	*p*	IPTW analysis groups	*p*
28-day mortality	−5.8% (−8.9% to −2.7%)	<0.001	−0.7% (−4.7% to3.1%)	0.601	−3.5% (−8.8% to1.7%)	0.180
In-hospital mortality	−7.3% (−10.7% to −3.9%)	<0.001	−1.0% (−5.4% to3.4%)	0.495	−3.6% (−9.4% to 2.1%)	0.217

Abbreviation: IPTW, inverse probability of treatment weighting.

Finally, we used propensity scores to adjust for patient background characteristics, but unmeasured confounders may have biased the results.

5. Conclusions

In conclusion, there were no significant differences in 28-day mortality and in-hospital mortality between azithromycin plus β-lactam and levofloxacin plus β-lactam for severe CAP patients.

Ethical approval and consent to participate

The study was approved by the Institutional Review Board of the University of Tokyo. Informed consent was waived because of the anonymous nature of the data.

Consent for publication

Not applicable.

Availability of data and materials

Data cannot be made publicly available for ethical reasons as the data are patient data. The data are available to interested researchers upon reasonable request to the corresponding author, pending ethical approval.

Conflicts of interest

The authors have disclosed that they do not have any potential conflicts of interest.

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Authorship statement

All authors contributed the design of the study. JS and YS take responsibility for the integrity of the data and accuracy of the data analysis. JS wrote the manuscript and YS helped to revise the manuscript. SH, HM, TS, YM, TY, and HY directly participated in the planning, execution, or analysis of the study. All authors read and approved the final manuscript. All authors meet the ICMJE authorship criteria.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.05.027.

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