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ORIGINAL RESEARCH

Effects of Broad-Spectrum Antimicrobials on Patients with Community-Acquired Pneumonia with Low Risk for Drug-Resistant Pathogens: Historical Cohort Study in Japan

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ABSTRACT

***Introduction*:** Broad-spectrum antimicrobials are commonly administered for community-acquired pneumonia (CAP); however, unnecessary administration may cause adverse events and poor outcomes. This study aimed to understand the impact of broad-spectrum anti-pseudomonal β-lactam use on clinical outcomes and healthcare resource utilization (HCRU) in inpatients with CAP and a low risk of drug-resistant pathogens (DRPs).

***Methods*:** This historical cohort study reviewed Japan's hospital claims database (January to December of 2018) and included inpatients aged ≥ 20 years who received intravenous antimicrobial therapy for CAP. Those with high DRP risk were excluded. According to the initial antimicrobial regimen, patients were divided into broad-spectrum (anti-pseudomonal β-lactam therapy) and narrow-spectrum (non-anti-pseudomonal β-lactam therapy) groups. This study evaluated 30-day hospital mortality as a primary outcome using inverse probability of treatment weighting (IPTW) to adjust for differences between both groups and HCRU as an exploratory analysis.

***Results*:** A total of 15,617 patients were analyzed (2627 in the broad-spectrum group and 12,990 in the narrow-spectrum group). In the broad-spectrum group, the 30-day mortality rate was 10.6%, which was higher than that in the narrow-spectrum group (5.3%). Furthermore, it was associated with an increased 30-day mortality compared with the narrow-spectrum group after IPTW (adjusted odds ratio, 1.77; 95% confidence interval, 1.52–2.06; $p < 0.001$). The mean inpatient cost was USD 6139 and USD 5184 for the broad- and narrow-spectrum groups, respectively.

***Conclusions*:** The initial use of anti-pseudomonal β-lactams for CAP with low DRP risk is associated with poor outcomes, including death and high HCRU. Thus, initial

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antimicrobials should be judiciously selected for CAP management.

Keywords: Community-acquired pneumonia; Anti-pseudomonal β-lactams; Mortality; Healthcare resource utilization

Key Summary Points

Why carry out this study?

Previous studies have affirmed that prescribing broad-spectrum antimicrobials for patients with community-acquired pneumonia (CAP) is associated with adverse events. However, only a few studies have examined the impact of the initial use of anti-pseudomonal β-lactams on mortality and other outcomes using large-scale databases in patients with CAP and a low risk of drug-resistant pathogens (DRPs).

What was learned from the study?

Using a large-scale hospital claims database, this study showed that anti-pseudomonal β-lactam use as the initial treatment was associated with higher 30-day mortality and healthcare resource utilization, including hospitalization costs, in patients hospitalized for CAP with low DRP risk.

How might this study affect research, practice or policy?

These findings support the importance of judiciously selecting broad-spectrum antimicrobials, such as anti-pseudomonal β-lactam, for the initial management of CAP.

INTRODUCTION

Community-acquired pneumonia (CAP) in adults causes high mortality and morbidity rates worldwide. The short-term (30-day) mortality rate for hospitalized patients ranges from 4.0% to 18.0%; however, for patients in the intensive care unit (ICU), it can reach 50% [1].

Numerous microbial pathogens, including bacteria and viruses, have been associated with CAP [2, 3]. However, a previous large-scale population-based study on adult inpatients with CAP (2010–2012) in the US revealed that a pathogen was detected only in 38% of patients using existing diagnostic tests in a study population with radiographic evidence of pneumonia and specimens available for both bacterial and viral testing [4]. This finding indicates the current limitations of diagnostics and challenges in optimal treatment based on microbiological results, which often warrant empirical antimicrobial use as the initial treatment.

In real-world settings, empirical antimicrobial treatment for CAP is challenging. Excessively broad-spectrum antibiotic therapy has also been associated with adverse outcomes [5].

Several studies have investigated the effect of broad-spectrum antimicrobials on mortality in patients with CAP [5–8]. In Japan, a recent study revealed that initial extended-spectrum antibiotic use was associated with increased 30-day mortality compared with that of standard therapy in 159 patients with CAP and low drug-resistant pathogens (DRPs) risk [7]. Another US retrospective cohort study involving 88,605 patients hospitalized for community-onset pneumonia (COP) in the US Veterans Health Administration healthcare system to examine the impact of empirical anti-methicillin-resistant *Staphylococcus aureus* (MRSA) therapy was significantly associated with an increased adjusted risk for mortality and other outcomes, such as kidney injury, *Clostridioides difficile* infection (CDI) and DRP infections [8].

This therapy was administered to 33,632 (38%) patients; compared with the standard therapy alone, empirical anti-MRSA therapy combined with standard therapy was significantly associated with an increased adjusted mortality risk (adjusted risk ratio, 1.4; 95% CI 1.3–1.5). This study also showed that the empiric usage of anti-MRSA therapy had a negative impact on other outcomes, such as increased rates of kidney injury, CDI, vancomycin-resistant *Enterococcus* spp. infections and Gram-negative rod infections [7, 9].

However, studies examining the impact of the initial use of anti-pseudomonal β-lactams on mortality and other outcomes with large-scale databases in patients with CAP and low DRP risk are still limited.

Therefore, the main objective of this study is to determine whether anti-pseudomonal β-lactams impact mortality and healthcare resource utilization (HCRU) compared with non-anti-pseudomonal β-lactam therapy in patients with CAP at low DRP risk. In this context, CAP refers to pneumonia acquired outside of the hospital settings [10]. In Japan, nursing and healthcare-associated pneumonia (NHCAP), healthcare-associated pneumonia (HCAP) modified for the Japanese healthcare system has been proposed by the Japanese Respiratory Society [11–13]. This category of pneumonia unique to Japan was also included as CAP in this study.

METHODS

Study Design and Participants

This historical cohort study analyzed data from a hospital database in Japan from January 2018 to December 2018. This study aimed to compare outcomes between an exposure cohort (broad-spectrum group), receiving broad-spectrum anti-pseudomonal β-lactams against *Pseudomonas aeruginosa*, and a comparison cohort (narrow-spectrum group), receiving narrow-spectrum non-anti-pseudomonal β-lactam therapy. This study was conducted using a new user design, therefore, participants were defined as newly received therapy.

Cohort Entry Date

The cohort entry date (day 0) was set on the date of admission to the hospital for CAP and antimicrobial treatment initiation on the same day in 2018.

Eligibility: Inclusion and Exclusion Criteria

This study included patients who met the eligibility criteria aged ≥ 20 years on day 0, who were hospitalized with CAP, and started on injectable antimicrobial therapy. CAP was defined as a diagnosis of CAP at the time of hospitalization. This study used the following diagnosis codes from the International Classification of Diseases, 10th Revision (ICD-10): pneumonia (J12.x–J18.x)13, aspiration pneumonia (J690, J698) and aspiration in the other post-treatment respiratory disorders (J958). In accordance with previous research [14], this study excluded patients with the following potential risk factors of DRP related to *P. aeruginosa*: patients who were diagnosed with *P. aeruginosa* (A048, A415, A498, G008, H602, J151, P235, and P368) [day − 90 to − 1] and those who were administered intravenous antimicrobials [− 90 to − 1].

Patients with a history of recent hospitalization [day − 90 to − 1], immunocompromised patients (hematological malignancies, neutropenia, steroid use, use of immunosuppressants and diagnosis of HIV) [day − 90 to 0], patients taking gastric acid-suppressing drugs (H2 blockers, proton pump inhibitors) [day − 90 to 0], patients requiring tube feeding [day − 90 to 0], patients with hypoalbuminemia [the same month with day 0] and patients requiring a ventilator on admission [day 0] were excluded for the study. This study also excluded patients with prior CAP episodes [day − 90 to − 1], those who underwent anti-MRSA treatment recently [day − 90 to − 1], and those who had no specific data on pneumonia severity and NHCAP [day 0]; moreover, patients who were administered specific antimicrobials (aminoglycosides, macrolides, tetracyclines, and fluoroquinolones) [day 0] were also excluded. Those who were prescribed both drugs that corresponded to the exposure and comparison groups on the cohort entry date [day 0] were excluded as well (Supplementary Fig. 1).

Definition of Exposure and Comparison

The study categorized patients into two groups according to their antibiotic prescriptions at hospital admission (day 0): the broad-spectrum and narrow-spectrum groups.

Patients belonged to the broad-spectrum group if they were prescribed broad-spectrum β-lactam antibiotics with anti-*P. aeruginosa* effect. These antibiotics contained any of the following: piperacillin hydrate/tazobactam (Pip/Taz), ceftazidime hydrate, cefepime hydrochloride hydrate, cefozopran hydrochloride, cefoperazone sodium/sulbactam sodium, meropenem hydrate, imipenem hydrate/cilastatin sodium and doripenem hydrate.

Conversely, patients were included in the narrow-spectrum group if they were prescribed β-lactam antibiotics without the anti-*P. aeruginosa* effect. The details of antibiotics are in supplementary documents.

Although some approaches consider medication switching, detailed switching would complicate interpretation. In addition, initial pneumonia treatment is rarely switched within a short period of time to confirm efficacy. Hence, this study conformed to the Intention-to-Treat (ITT) principle.

Data Source

The study population data were extracted from the Medical Data Vision Co., Ltd. database (MDV-DB; https://en.mdv.co.jp/) containing the administrative data of approximately 44 million patients who were treated at 485 acute-care hospitals and tracked using the Japanese Diagnosis Procedure Combination (DPC)/Per-Diem Payment System. Most acute-care hospitals in Japan are DPC-enrolled, with approximately 45% of the 1764 DPC hospitals in Japan included in the MDV-DB as of April 1, 2022. MDV-DB is not an insurer's database; therefore, it cannot be traced if the patient is transferred or switched to a different hospital [15].

Study Outcomes and Covariates

The primary outcome was hospital mortality within 30 days of admission. Thirty-day mortality has been widely adopted in previous studies assessing the impact of broad-spectrum antibiotics on patient outcomes in CAP, reinforcing its validity as a key endpoint [6–8]. Given the strong precedent set by clinical guidelines and prior research, we used 30-day mortality as the most appropriate and widely accepted measure of CAP outcomes. If no outcome had occurred and the date of the last visit was before the end date of the 30-day period, it was treated as censored on the date of the last visit. The same description was used for the secondary outcome to determine whether CDI occurred. In this study, CDI was defined as a confirmed diagnosis of *C. difficile* enteritis or a positive qualitative test for *C. difficile* antigen and a prescription of vancomycin (oral) or metronidazole (oral/injection); the date of CDI onset was the first day of the diagnosis, testing, and prescription.

The covariates obtained on day 0 were as follows: data regarding sex, age, nursing and NHCAP, oxygen administration and facility information such as additional healthcare reimbursement for infection prevention and control (ICT/AST) and hospital size (≤ 199, 200–499 and ≥ 500 beds), ICU admission, vasopressors use. NHCAP was confirmed by medical staff and reported according to DPC format.

Comorbidity was defined as the presence or absence of a disease diagnosis corresponding to the Charlson Comorbidity Index between days − 90 and 0. Hemodialysis and central venous nutrition use were defined between days − 90 and 0. To classify pneumonia severity, this study uses the A-DROP score ranging from 0 to 5. Patients with scores of 0–2 points were classified as the non-severe group and those with scores of 3–5 points as the severe group [11, 13]. These variables were referred to as the pneumonia severity classification values assessed on admission (day 0). Patients with missing data for NHCAP and A-DROP were excluded. Only those with complete data were included in the analysis. Other covariates were treated as 0 if they were not recorded.

Statistical Analyses

This study initially described the background attributes of both groups and the two analyses that were performed. This study considered the accumulated incidence rate by time and odds

ratio (OR) of hospital mortality as a primary analysis and the CDI as a secondary analysis. The study conducted inverse probability of treatment weighting (IPTW) using stabilized weights to address extreme weight values (outliers), which estimated the average treatment effect using the propensity scores of the covariates by a logistic regression model [16]. IPTW was employed to balance each group and ensure it was performed under comparable conditions. Selected covariates were sex, age, comorbidities, NHCAP, A-DROP score, oxygen administration, facility information (ICT/AST) and hospital size, ICU admission, vasopressors use, hemodialysis and central venous nutrition use. A-DROP was treated as a categorical variable. The aggregation of baseline covariates was calculated before and after the IPTW adjustment and evaluated the balance between both groups by standardized mean difference (SMD) less than 0.1 as a good adjustment.

In addition, the study depicted Kaplan–Meier curves for hospital mortality and CDI occurrence in the population after the IPTW. These analyses were conducted in subgroups based on pneumonia severity. The detail of the sample calculation is noted in supplementary documents.

Exploratory Analysis of HCRU

As an exploratory analysis, this study described a breakdown of the HCRU and associated costs and the duration of hospital stay (LOS) of each patient during hospitalization. The method of calculating medical expenses was to sum up the costs listed in the claims data for hospitalization fees, examination fees, drug cost, treatment cost, and others. Obtained data on HCRU occurring from the start of day 0 to the end of the discharge date.

This study extracted patient data and created analysis datasets using SQL against a database built on AWS Athena. The software R (version 4.2.1) was used for all statistical analysis.

Ethical Approval

This study did not require patient consent or approval from an institutional review board or an independent ethics committee because the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to studies exclusively on anonymized data. This study is STROBE and RECORD-PE compliant.

RESULTS

Of the 88,948 reviewed patients who were hospitalized for pneumonia and administered antimicrobial injections, a total of 15,617 met the inclusion criteria of this study, with 2627 in the broad-spectrum group and 12,990 in the narrow-spectrum group (Fig. 1).

Table 1 presents the characteristics of the study participants. The mean (SD) age was 80.5 (11.4) years in the broad-spectrum group and 80.8 (12.4) years in the narrow-spectrum group, with males accounting for 59.9% and 56.0%, respectively. Some variables had a SMD of over 0.1, indicating imbalance in both groups. These variables were chronic respiratory disease, pneumonia type (NHCAP), pneumonia severity (A-DROP) and oxygen administration. However, after IPTW weighting, all characteristics were balanced. Supplementary Table 1 lists the types of antimicrobial injectable drugs used at the cohort entry date (day 0) in each group. Pip/Taz was administered to 68.3% of patients in the broad-spectrum group. In the narrow-spectrum group, 54.7% received ampicillin sodium/sulbactam sodium and 41.1% received ceftriaxone sodium hydrate. Supplementary Table 2 lists the breakdown of the disease names of participants. There were very few patients who had a virus in both groups.

Primary Outcome: Hospital Mortality

Before IPTW weighting, mortality was higher in the broad-spectrum group overall (10.6% in the

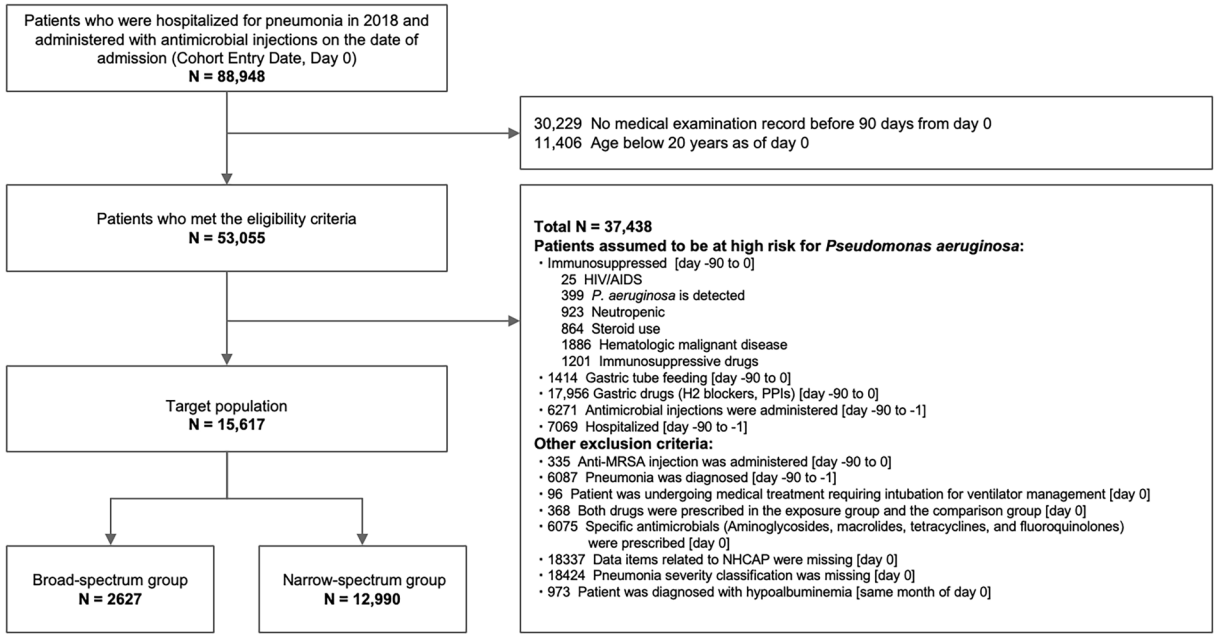

Fig. 1 Patient selection flow. *MRSA* methicillin-resistant *Staphylococcus aureus, NHCAP* nursing and healthcare-associated pneumonia

broad-spectrum group, 5.3% in the narrow-spectrum group), non-severe (5.0% and 2.9%, respectively) and severe (21.0% and 12.0%, respectively) subgroups (Table 2). Furthermore, the OR of the broad-spectrum group was approximately twice higher than that of the narrow-spectrum group in the overall (OR: 2.13; 95% CI 1.84–2.46), non-severe (OR: 1.77; 95% CI 1.38–2.27) and severe (OR: 1.94; 95% CI 1.60–2.34) subgroups. The trend remained unchanged even after IPTW weighting (Table 3). Kaplan–Meier curves are depicted in Fig. 2, and the log-rank test indicated significant differences in the overall and other subgroups.

Secondary Outcome: CDI Incidence

Before IPTW weighting, CDI incidence was slightly higher in the broad-spectrum group than in the narrow-spectrum group overall (1.0% and 0.8%, respectively), non-severe (0.8% and 0.7%, respectively) and severe (1.5% and 1.3%, respectively) subgroups (Table 2). However, there is no evidence of an association between antibiotics and CDI, as shown in Table 2. Regarding CDI, the OR showed no significant differences before IPTW in the overall (OR: 1.25; 95% CI 0.80–1.88), non-severe (OR: 1.14; 95% CI 0.60–2.01) and severe (OR: 1.21; 95% CI 0.63–2.16) subgroups and after IPTW, the same trends were observed (Table 3). The log-rank test indicated no significant differences in the CDI group (Fig. 2).

HCRU

Table 4 shows the HCRU for average hospitalization costs and LOS, aggregated by patients before IPTW weighting.

Table 1 Participant characteristics (before and after IPTW)

	Before IPTW weighting					After IPTW weighting		
	Broad-spectrum group ($N = 2627$)		Narrow-spectrum group ($N = 12,990$)		SMD	Broad-spectrum group ($N = 2452$)	Narrow-spectrum group ($N = 12,944$)	SMD
Sex: male (*n*, %)	1574	59.9%	7278	56.0%	0.08	56.2%	56.7%	0.01
Age (mean, SD)	80.5	11.4	80.8	12.4	0.02	80.7	80.7	0.00
Comorbidities (*n*, %)								
Myocardial infarction	61	2.3%	329	2.5%	0.01	2.4%	2.5%	0.00
Congestive heart failure	648	24.7%	3185	24.5%	0.00	24.5%	24.5%	0.00
Peripheral vascular disease	157	6.0%	640	4.9%	0.05	5.2%	5.1%	0.01
Cerebrovascular disorder	465	17.7%	2395	18.4%	0.02	18.3%	18.3%	0.00
Dementia	434	16.5%	2330	17.9%	0.04	17.5%	17.7%	0.00
Chronic respiratory disease	841	32.0%	3418	26.3%	0.13	27.5%	27.3%	0.00
Rheumatic diseases	28	1.1%	85	0.7%	0.05	0.7%	0.7%	0.00
Peptic ulcer	253	9.6%	1039	8.0%	0.06	8.3%	8.3%	0.00
Mild liver disease	187	7.1%	842	6.5%	0.03	6.6%	6.6%	0.00
Diabetes without chronic complications	369	14.0%	1652	12.7%	0.04	13.1%	13%	0.00
Diabetes with chronic complications	120	4.6%	608	4.7%	0.01	4.8%	4.7%	0.01
Hemiplegia	22	0.8%	97	0.7%	0.01	0.7%	0.8%	0.00
Kidney disease	232	8.8%	943	7.3%	0.06	7.5%	7.5%	0.00
Malignant tumors, including lymphoma and leukemia (excluding malignant neoplasms of the skin)	423	16.1%	1820	14.0%	0.06	14.6%	14.4%	0.01
Moderate or severe liver disease	6	0.2%	25	0.2%	0.01	0.2%	0.2%	0.01
Metastatic solid tumor	90	3.4%	296	2.3%	0.07	2.5%	2.5%	0.00
Pneumonia type (*n*, %)								
NHCAP	1003	38.2%	4300	33.1%	0.11	33.9%	34%	0.00
Pneumonia severity A-DROP (*n*, %)								
Score 0	216	8.2%	1096	8.4%	0.01	8.4%	8.4%	0.00
Score 1	658	25.0%	3918	30.2%	0.12	29.2%	29.3%	0.00
Score 2	834	31.7%	4581	35.3%	0.08	34.7%	34.7%	0.00
Score 3	650	24.7%	2604	20.0%	0.11	20.9%	20.8%	0.00
Score 4	228	8.7%	682	5.3%	0.14	5.8%	5.8%	0.00

Table 1 continued

	Before IPTW weighting					After IPTW weighting		
	Broad-spectrum group (*N* = 2627)		Narrow-spectrum group (*N* = 12,990)		SMD	Broad-spectrum group (*N* = 2452)	Narrow-spectrum group (*N* = 12,944)	SMD
Score 5	41	1.6%	109	0.8%	0.07	1%	1%	0.00
Oxygen administration (*n*, %)	1475	56.1%	6462	49.7%	0.13	50.7%	50.8%	0.00
ICT/AST (*n*, %)	2608	99.3%	12,940	99.6%	0.05	99.6%	99.6%	0.00
Hospital size (*n*, %)								
≤ 199 beds	333	12.7%	1489	11.5%	0.04	11.6%	11.7%	0.00
200–499 beds	1713	65.2%	8531	65.7%	0.01	65.9%	65.6%	0.01
≥ 500 beds	581	22.1%	2970	22.9%	0.02	22.5%	22.7%	0.01
ICU admission (*n*, %)	81	3.1%	277	2.1%	0.06	2.3%	2.3%	0.001
Vasopressors (*n*, %)	31	1.2%	51	0.4%	0.09	0.5%	0.5%	0.001
Hemodialysis (*n*, %)	20	0.8%	47	0.4%	0.05	0.4%	0.4%	0.001
Central venous nutrition (*n*, %)	25	1.0%	36	0.3%	0.09	0.4%	0.4%	0.001

Values are expressed as numbers (percentages) unless otherwise stated. The item with duplicate counts (Drugs for Immunosuppression/Chemotherapy) is shown in frequencies only

SMD standardized mean difference, *IPTW* inverse probability of treatment weighting, *NHCAP* nursing- and healthcare-associated pneumonia, *A-DROP* a scoring system with the variables age, dehydration and respiratory failure, orientation disturbance and blood pressure, *ICU* intensive care unit

IPTW inverse probability of treatment weighting

In each subgroup, the broad-spectrum group had higher costs and a longer LOS than the narrow-spectrum group. Overall, the cost was USD 6139 in the broad-spectrum group and USD 5184 in the narrow-spectrum group. The broad-spectrum group also had higher drug consumption than the narrow-spectrum group. Additionally, the LOS was 23.1 and 19.8 days in the broad-spectrum and narrow-spectrum group, respectively. Among the population of 65 years and over, the cost was USD 6235 and USD 5359 and the LOS was 23.7 and 20.6 days in the broad-spectrum and narrow-spectrum group, respectively. The HCRU components, such as the hospitalization fee, examination fee, drug cost, and treatment cost, are detailed in Supplementary Table 3. The broad-spectrum group scored higher than the narrow-spectrum group in all categories of HCRU.

DISCUSSION

This study investigated the impact of the initial use of anti-pseudomonal β-lactam therapy in 15,617 patients hospitalized for CAP with low DRP risk, using data from a nationwide hospital claims database. Based on previous studies [5–9], our study concentrated on examining the effects of anti-pseudomonal β-lactam antimicrobials as broad-spectrum therapy and comparing them with the effects of narrow-spectrum therapy. To the best of the knowledge of the authors, this study is the first to reveal the negative impact of the initial administration of anti-pseudomonal antimicrobials on outcomes such as mortality, CDI, and HCRU in patients hospitalized with CAP with a low DRP risk. This study has excluded quinolones from the analysis because

Table 2 Number of deaths and CDI by severity (before IPTW)

		N	Number of events	%
Mortality				
Overall	Broad-spectrum group	2627	278	10.6
	Narrow-spectrum group	12,990	684	5.3
Non-severe	Broad-spectrum group	1708	85	5.0
	Narrow-spectrum group	9595	275	2.9
Severe	Broad-spectrum group	919	193	21.0
	Narrow-spectrum group	3395	409	12.0
CDI				
Overall	Broad-spectrum group	2627	27	1.0
	Narrow-spectrum group	12,990	107	0.8
Non-severe	Broad-spectrum group	1708	13	0.8
	Narrow-spectrum group	9595	64	0.7
Severe	Broad-spectrum group	919	14	1.5
	Narrow-spectrum group	3395	43	1.3

CDI Clostridioides difficile infection, *IPTW* inverse probability of treatment weighting

they could be used to treat atypical pneumonia in CAP management [10] and focused on anti-pseudomonal β-lactam therapies.

The 30-day mortality rate was 10.6% in those who initially received anti-pseudomonal β-lactam therapy (broad spectrum) compared with 5.3% in those who did not (narrow spectrum). Thus, the initial use of broad-spectrum treatment was associated with an increased 30-day mortality rate in contrast to that in the narrow-spectrum group after IPTW. This trend was observed regardless of pneumonia severity. Furthermore, increased cost and HCRU were observed in the broad-spectrum therapy group. Notably, the most commonly used anti-pseudomonal β-lactam antimicrobial in this study was Pip/Taz.

Likewise, a recent nationwide DPC study from Japan examined the impact of anti-MRSA therapy in older adults with aspiration pneumonia and showed that the initial use of anti-MRSA therapy was associated with higher mortality. Comparatively, another Japanese study revealed a considerably lower rate of anti-MRSA agent use (0.93% and 0.42% in those with and without respiratory failure, respectively) than the previous US study [9]. Based on these findings, the present study intentionally focused on intravenous anti-pseudomonal antimicrobials, assuming a relatively small percentage of anti-MRSA drug use in the management of inpatients with CAP.

A previous retrospective observational cohort study conducted in four US institutions examined 1995 adults with COP admitted to hospital emergency departments. Broad-spectrum antibiotics were prescribed to 39.7% of the patients, but DRPs were recovered in only 3%. It showed that any broad-spectrum antibiotic use (either anti-MRSA or anti-pseudomonal drugs) as initial therapy was associated with increased 30-day mortality risk (OR, 3.8; 95% CI 2.5–5.9; $p<0.001$) and higher 30-day mortality after IPTW (adjusted OR, 1.77; 95% CI 1.52–2.06; $p<0.001$). In addition, broad-spectrum antibiotic use was associated with longer LOS, higher cost, and increased CDI. However, this previous study did not exclude patients at high risk of DRPs [8].

Most recently, a Japanese study evaluated broad-spectrum antibiotics for CAP with low DRP risk [7]. Of the 416 examined inpatients with CAP with low DRP risk, 257 underwent standard therapy, whereas 159 underwent broad-spectrum therapy, as an initial antimicrobial therapy upon hospitalization. Broad-spectrum therapy was associated with increased 30-day mortality compared with standard therapy

Table 3 Odds ratio and 95% confidence intervals for mortality and CDI in the association between antibiotic selection and prognosis (before and after IPTW)

	Before IPTW weighting			After IPTW weighting		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Mortality						
Overall	2.13	1.84–2.46	< 0.001	1.76	1.52–2.05	< 0.001
Non-severe	1.77	1.38–2.27	< 0.001	1.76	1.37–2.27	< 0.001
Severe	1.94	1.60–2.34	< 0.001	1.85	1.52–2.24	< 0.001
CDI						
Overall	1.25	0.80–1.88	0.30	1.24	0.80–1.91	0.34
Non-severe	1.14	0.60–2.01	0.66	1.21	0.65–2.23	0.55
Severe	1.21	0.63–2.16	0.55	1.27	0.69–2.35	0.44

CDI Clostridioides difficile infection, *CI* confidence interval, *OR* odds ratio, *IPTW* inverse probability of treatment weighting

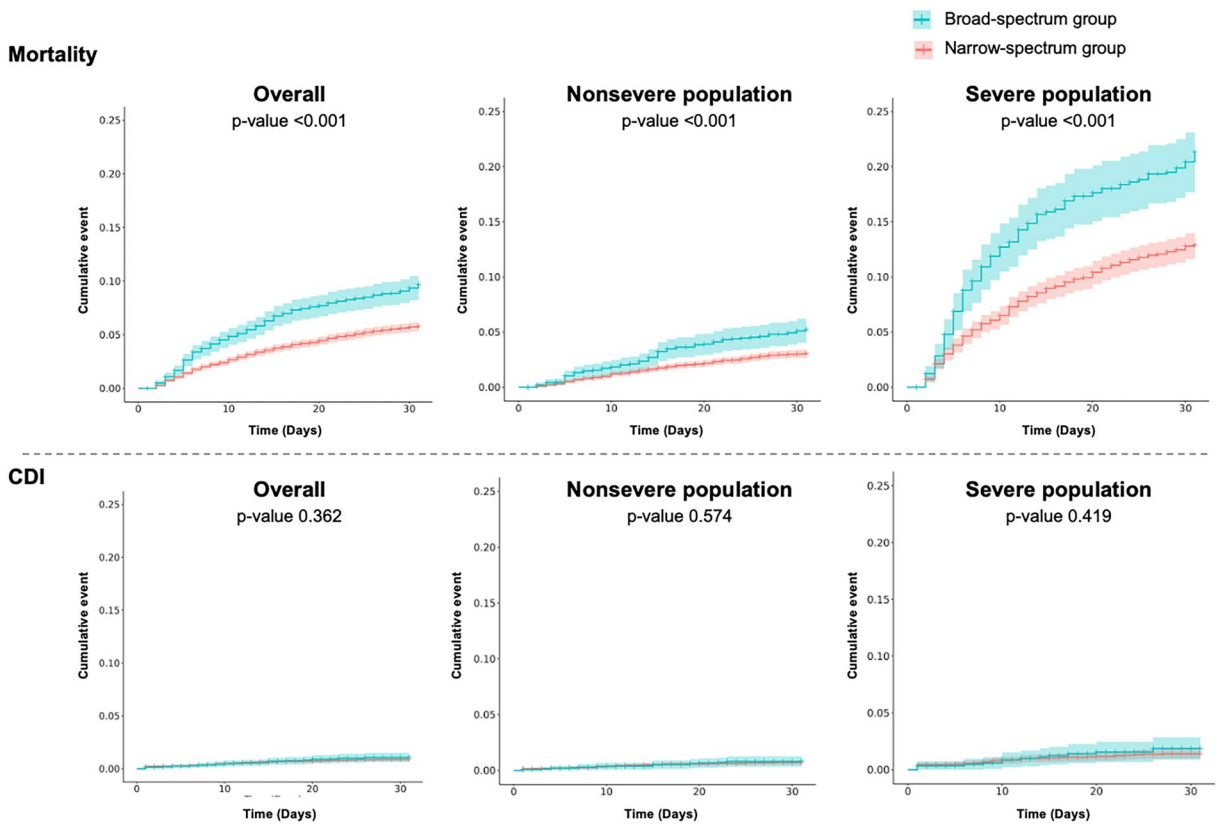

Fig. 2 Kaplan–Meier curve for mortality and *Clostridioides difficile* infection (CDI) in the population after the IPTW by severity. For pneumonia severity, A-DROP score of 0–2 points was classified as non-severe group and scores of 3–5 points as severe group

Table 4 Healthcare resource usage for average hospitalization costs and length of hospital stay before IPTW

	Broad-spectrum group			Narrow-spectrum group		
	N	Average hospitalization		*N*	Average hospitalization	
		Cost	LOS		Cost	LOS
Overall	2627	6139	23.1	12,990	5184	19.8
Sex						
Male	1574	6277	22.8	7278	5236	19.7
Female	1053	5932	23.5	5712	5119	20
Age						
< 65 years	211	5037	16.5	1080	3252	11.5
≥ 65 years	2416	6235	23.7	11,910	5359	20.6
Comorbidities						
Myocardial infarction	61	6832	26.3	329	5253	18.4
Congestive heart failure	648	6734	25.2	3185	5856	21.9
Peripheral vascular disease	157	6714	25	640	5703	20.9
Cerebrovascular disorder	465	7153	27.2	2395	6027	23.4
Dementia	434	6900	27.8	2330	6148	24.5
Chronic respiratory disease	841	5772	21.4	3418	4799	17.9
Rheumatic diseases	28	5952	20.1	85	4166	15.5
Peptic ulcer	253	6699	24.9	1039	5333	19.6
Mild liver disease	187	5947	22.3	842	4698	17.8
Diabetes without chronic complications	369	6413	23.9	1652	5221	19.4
Diabetes with chronic complications	120	5999	20.7	608	5607	20.7
Hemiplegia or hemiplegia	22	7770	29.4	97	7085	27.3
Kidney disease	232	7075	23.8	943	5636	20.3
Malignant tumors, including lymphoma and leukemia (excluding malignant neoplasms of the skin)	423	6054	22.2	1820	5135	19.4
Moderate or severe liver disease	6	6933	16.7	25	4578	18.1
Metastatic solid tumor	90	5707	20.6	296	5161	18.9
Pneumonia type						
Non-NHCAP	1003	6737	25.8	4300	5979	23.4
NHCAP	1624	5769	21.4	8690	4791	18.1

Table 4 continued

	Broad-spectrum group			Narrow-spectrum group		
	N	Average hospitalization		*N*	Average hospitalization	
		Cost	LOS		Cost	LOS
Severity (A-DROP)						
Score 0	216	3789	14.5	1096	2906	10.9
Score 1	658	5346	20.9	3918	4313	16.9
Score 2	834	6372	24.5	4581	5390	20.8
Score 3	650	6937	25.5	2604	6473	24.3
Score 4	228	7455	25.7	682	7291	27.2
Score 5	41	6527	22.5	109	6778	24.7
Oxygen administration						
Yes	1475	6749	25.2	6462	5900	22
No	1152	5357	20.5	6528	4476	17.7
ICT/AST	2608	6143	23.1	12940	5184	19.8
Hospital size						
≤ 199 beds	333	6500	25.1	1489	5485	22.6
200–499 beds	1713	6125	23.6	8531	5221	20.2
≥ 500 beds	581	5972	20.5	2970	4927	17.3

The cost were converted at 151.34 yen to the US dollar (as of March 30, 2024)

CDI Clostridioides difficile infection, *LOS* length of stay, *NHCAP* nursing- and healthcare-associated pneumonia, *A-DROP* a scoring system with the variables age, dehydration and respiratory failure, orientation disturbance, and blood pressure

(adjusted OR: 2.82; 95% CI 1.20–6.66) implying that broad-spectrum antibiotics are harmful in patients with CAP with low DRP risk. However, the broad-spectrum therapy in the previous study included both intravenous anti-pseudomonal antimicrobials and anti-MRSA drugs; thus, the extent of the effects of anti-pseudomonal antimicrobials on patient outcomes remains unclear. In addition, the sample size of the previous study was relatively small, including only four medical institutions in Japan [7].

Although this study did not explore the causes of increased mortality and poor outcomes in the broad-spectrum group, several explanations have been proposed. CDI is one of the major nosocomial infections, often attributed to increased antibiotic use [17]. Previous studies have shown an increased CDI rate in inpatients with pneumonia taking broad-spectrum antimicrobials [5, 6, 8, 18]. In the US cohort study mentioned above, the evaluation of the effects of broad-spectrum antimicrobials, including anti-pseudomonal antimicrobials, on patients with CAP, the OR of CDI was approximately fourfold greater for those receiving broad-spectrum regimens, with statistical significance. In this study, the OR of CDI in the broad-spectrum group slightly increased, demonstrating no statistical significance. The differences in the OR of CDI in various studies would be multifactorial. Still, they could be partially attributable to different degrees of risk for CDI development specific to each antimicrobial agent [19–22].

Another possible explanation is acute kidney injury (AKI). Antibiotics are a common cause of drug-induced nephrotoxicity [23]. In CAP, a previous retrospective, multicenter cohort study of inpatients conducted in the US showed that the empirical use of anti-MRSA therapy was strongly associated with AKI. In this study, the most commonly used broad-spectrum antimicrobial was Pip/Taz. Although this study could not explore a causal relationship between antimicrobial use and AKI occurrence because of the limitations of the hospital claims database used, Pip/Taz is associated with AKI [24–27]. Previous studies have suggested an association between Pip/Taz and an increased risk of AKI, particularly when administrated with vancomycin [24–27], but a randomized clinical trial (Antibiotic Choice on Renal Outcomes ACORN) reported no significant difference in the risk of AKI for patients treated with Pip/Taz other treatments [28]. Semisynthetic penicillin such as Pip/Taz reportedly causes acute interstitial nephritis (AIN) [24]. Additionally, adults with CAP aged 65 years or older account for approximately 70% of Japan's aging society [29]. Our study is consistent with these findings, and the mean age of our study population was above 80 years.

Furthermore, gut dysbiosis caused by the adverse effects of antibiotics could impair pulmonary defense in the human microbiota, making hosts more susceptible to nosocomial pneumonia [30–33]. Additionally, one of the most recognized consequences of broad-spectrum antibiotic use is the risk of developing antimicrobial resistance (AMR) [6, 7, 34]. Although we could not capture AMR incidence because of the limitations of our hospital claims database, AMR could be a hypothetical explanation for increased mortality and HCRU [35].

This study has several limitations similar to previous studies using the MDV database [36–38]. First, the MDV database includes only hospitals under the DPC system. This study excludes small-scale hospitals, clinics, and medical institutions not covered by the DPC system and focuses mainly on acute-care hospitals.

The results of IPTW are generalizable only to populations similar to the study population. Therefore, the generalizability is limited to populations and environments similar to those included in the MDV database. Additionally, the generalizability of results using IPTW is constrained by the completeness and representativeness of the dataset and by the assumption that all relevant confounders are measured and appropriately modeled. This study did not include laboratory data (i.e., pathogens), these unmeasured variables might give disproportionate weight to individuals in underrepresented groups, reducing generalizability. The A-DROP score was included in our analysis; however, the details of each test value were not available in this study. SpO_2 is a crucial indicator of disease severity and could have been a valuable covariate. However, this study was based on hospital claims data, which did not consistently include SpO_2 values, except as one component of the A-DROP score at admission. Instead, we used oxygen administration as a surrogate marker of respiratory status. The 'R' component of A-DROP strictly refers to $SpO_2 \leq 90\%$ on room air. However, in routine clinical practice, when oxygen is administered, the decision to include 'R' is often based on the attending physician's estimation. Since health claims data do not provide direct SpO_2 values, our analysis relied on the recorded A-DROP score. Given the clinical importance of hypoxemia, we acknowledge the limitations of using administrative data without direct physiological measurements and recognize that this may impact the interpretation of our findings. These residual confounding might lead to misclassification and distort the comparative validity. However, unlike matching, the IPTW method does not exclude off-support individuals from the analysis. Hence, it is useful that it is possible to estimate the effect on the entire population represented by the sample [16]. It should be carefully understood that the results about the association between clinical outcome and anti-pseudomonal use. It might not eliminate the possibility of reverse causation, as the decision to use broad-spectrum antibiotics may have been influenced by unmeasured severity factors, which could contribute to higher 30-day mortality. These factors could contribute to both higher 30-day mortality and increased medical

costs, rather than the use of antipseudomonal agents itself being the direct cause.

Second, MDV data analyses have a limitation for identifying the pathogenic microorganisms and the duration of antibiotic exposure. These might affect misclassification for both groups, and the data definitions will need to be considered. For example, ICD-10 code-based definitions of the CAP population do not necessarily reflect the actual clinical diagnosis. However, we used ICD-10 codes validated in previous MDV data analyses for CAP to mitigate this concern. In addition, the population may be stringent excluded of *P. aeruginosa*. Specifically, because many of the subjects had used antimicrobial agents in the past (6271 antimicrobial injections were administered) or had received gastric drugs (17,956 H2 blockers, PPIs), it is likely that many older people were excluded from the population. Furthermore, 26.3%–32.0% of the population had chronic respiratory disease, although they were not excluded from the analysis, and this was a conservative setting. However, a difference was observed in the results, which is important. Third, patients transferred to other hospitals were censored because the MDV database does not capture such cases.

Moreover, this study intentionally used data before the global COVID-19 pandemic due to the disruption caused in the national healthcare service [39]. In Japan, the pandemic reported its first case in January 2020, until May 2023, when the government reclassified COVID-19 as a Category V infectious disease, the same as the seasonal influenza [40]. Future studies should clarify the potential impact of the pandemic in HCRU including antimicrobial usage in CAP patients, and re-evaluating the impact of broad-spectrum antimicrobials on CAP in the post-pandemic era. Furthermore, there is an important area for future research on the exploration of the impact of microbiome alterations on treatment outcomes related to the use of ß-lactams for the treatment of adult CAP, particularly comparing broad-vs. narrow-spectrum β lactams. Finally, this study followed the ITT principle to study the actual clinical situation. The ITT analysis includes every subject according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that occurs after randomization. Therefore, the drugs may have been switched during the follow-up period. However, this study evaluated the impact of the initial empiric administration of antimicrobials and showed that the initial administration of anti-pseudomonal antimicrobials was associated with poor outcomes. If the drug is switched for some reason, such as adverse reactions, it is likely to happen early in most cases, and in this study, patients who used broad- and narrow-spectrum on the same day were excluded. Hence, the impact of the switching drug is considered small.

In addition, this analysis has not been adjusted for the use of antifungal and antiviral treatments. While our primary focus was on broad-spectrum β-lactams, we recognize that these additional therapies may have influenced the outcomes. Further research is needed to evaluate their potential impact.

CONCLUSIONS

The initial use of anti-pseudomonal β-lactams for CAP with a low DRP risk is associated with higher mortality and HCRU, including inpatient costs. Therefore, to mitigate these negative outcomes in CAP management, healthcare providers should avoid unnecessary prescription of anti-pseudomonal β-lactams for patients with low DRP risk.

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Declarations

Conflict of Interest. Takahiro Takazono, Naoki Hosogaya, Naoki Iwanaga, Noriho Sakamoto, and Hiroshi Mukae have no conflicts of interest to disclose. Rie Ueno and Junichi Hirayama are employed at BioMérieux Ltd., while Yoshiyuki Saito and Masahiko Takemura work at Datack, Inc. Both companies are located in Japan.

Ethical Approval. This study did not require patient consent or approval from an institutional review board or an independent ethics committee because the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to studies exclusively on anonymized data. This study is STROBE and RECORD-PE compliant.

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