

# Impact and indication of early systemic corticosteroids for very severe community-acquired pneumonia

Motoi Ugajin  
Kenichi Yamaki  
Natsuko Hirasawa  
Takanori Kobayashi  
Takeo Yagi

Department of Respiratory Medicine,  
Ichinomiya-Nishi Hospital, Ichinomiya  
City, Aichi Prefecture, Japan

**Background:** The efficacy of systemic corticosteroids in community-acquired pneumonia (CAP) has not yet been confirmed. We prospectively investigated the clinical features of patients treated with early adjunctive systemic corticosteroids and its clinical impact in very severe CAP.

**Methods:** One hundred and one consecutive CAP patients having a pneumonia severity index of  $>130$  points were enrolled from August 2010 through February 2013. Early adjunctive systemic corticosteroids were defined as administration of systemic corticosteroids equivalent to prednisone of  $\geq 20$  mg/day added to initial antibiotics. The multivariate analysis was performed to evaluate the independent factors associated with mortality.

**Results:** Thirty-two patients (31.7%) died within 28 days of admission. Early adjunctive systemic corticosteroids were administered in 30 patients (29.7%), who more frequently had alteration of mental status, serious respiratory failure, or underlying lung diseases and received fluoroquinolones as initial antibiotics. In most patients treated with early adjunctive systemic corticosteroids, the dosage was less than 60 mg/day of an equivalent to prednisone by bolus intravenous infusion for a period shorter than 8 days. The occurrence of adverse events did not differ between the groups. Factors independently associated with mortality were blood urea nitrogen (hazard ratio [HR] 1.02, 95% confidence interval [CI] 1.00–1.04), serum albumin (HR 0.44, 95% CI 0.22–0.86), a requirement for intensive care (HR 4.93, 95% CI 1.75–13.87), and the therapy with early adjunctive systemic corticosteroids (HR 0.29, 95% CI 0.11–0.81).

**Conclusion:** Early adjunctive systemic corticosteroids may have an effect to reduce the mortality in very severe CAP, although a larger-scale study is necessary.

**Keywords:** pneumonia severity index, initial antibiotics, mortality, intensive care, community-acquired pneumonia, corticosteroids

## Introduction

Community-acquired pneumonia (CAP) remains a serious illness and a major cause of death. Former studies have shown that in patients with CAP, systemic inflammatory responses lead to poor clinical outcomes.<sup>1,2</sup> Therefore, attenuating systemic inflammatory responses is occasionally attempted in severe CAP. Corticosteroids are well known as anti-inflammatory agents and act at the genomic level.

In severe sepsis and septic shock, there is growing evidence that low-dose systemic corticosteroids may contribute to favorable clinical outcomes.<sup>3,4</sup> However, in CAP, the efficacy of systemic corticosteroids added to antibiotic therapy has not yet been confirmed. In a retrospective study, Garcia-Vidal et al reported that the administration of systemic corticosteroids contributed to the reduction of mortality in severe CAP.<sup>5</sup> In contrast, the randomized, double-blind, placebo-controlled study produced by Snijders

Correspondence: Motoi Ugajin  
Department of Respiratory  
Medicine, Ichinomiya-Nishi  
Hospital, I Hira, Kaimei,  
Ichinomiya City, 494-0001, Japan  
Tel +81 586 48 0077  
Fax +81 586 48 0038  
Email [ugarin2001@yahoo.co.jp](mailto:ugarin2001@yahoo.co.jp)

et al showed no beneficial effects of adjunctive corticosteroids in hospitalized CAP patients.<sup>6</sup>

Most of the previous placebo-controlled interventional CAP studies included a limited number of critically ill patients.<sup>6-9</sup> Therefore, the impact of adjunctive systemic corticosteroids on the prognosis of CAP has not yet been revealed. In current clinical practice, systemic corticosteroids are often added to the initial administration of antibiotics in some cases of very severe CAP, depending on the discretion of each pulmonologist.

In this single-center, prospective, and observational study, we investigated the clinical features of patients treated with early adjunctive systemic corticosteroids and impact of early adjunctive systemic corticosteroids on clinical outcomes in very severe CAP.

## Materials and methods

### Patients

Consecutive patients admitted to the Ichinomiya-Nishi hospital (a 400-bed teaching hospital in Ichinomiya City, Aichi, Japan) because of CAP, from August 2010 through February 2013, who had a pneumonia severity index (PSI) of >130 points (class 5)<sup>10</sup> on admission, were enrolled in this study. CAP was diagnosed in patients aged  $\geq 18$  years who were admitted from the community or a nursing home, had not been hospitalized in the 90 days before the start of the study, did not have any antibiotic exposure during the 14 days prior to enrollment, presented with a new radiographic infiltrate, and who showed at least two compatible clinical symptoms (body temperature  $>38^{\circ}\text{C}$ , productive cough, chest pain, shortness of breath, or crackles on auscultation). Patients were excluded if they were chronically immunosuppressed (chemotherapy, human immunodeficiency virus infection, therapy with corticosteroids, or other immunosuppressive agents).

Informed consent was obtained from all patients, according to the hospital's guidelines. This study protocol and consent procedure followed the statements of the Declaration of Helsinki, and was approved by the ethics committee of our hospital, called the Research Ethics Review Committee of Ichinomiya-Nishi Hospital (Study Number 25011).

### Methods and endpoints

Calculation of PSI, collection of venous blood samples, arterial blood gas analysis, microbiological sputum examination, and urinary antigen tests for *Streptococcus pneumoniae* (Alere BinaxNOW<sup>®</sup> S pneumoniae Antigen Card; Alere Inc, Waltham, MA, USA) and *Legionella pneumophila* serogroup 1 (Alere BinaxNOW<sup>®</sup> Legionella Urinary Antigen

Card; Alere Inc) were performed on admission for all CAP patients. Measurements of blood counts and levels of serum biochemical markers (C-reactive protein [CRP], blood urea nitrogen, albumin, glucose, sodium, and creatinine) were performed immediately after blood sampling. Serum CRP level was measured using a latex agglutination assay (N-Assay LA CRP-S, Nittobo Medical, Tokyo, Japan). Other biochemical markers were assayed using standard methods. Causative pathogens were diagnosed with the finding of 3+ growth in the sputum culture or the presence of antigen in urine.

Coexisting illnesses (heart failure, diabetes mellitus, cerebrovascular diseases, neoplastic diseases, chronic kidney diseases, advanced liver diseases, chronic obstructive pulmonary disease [COPD], and other lung diseases) were assessed by the treating pulmonologists.

Performance status before admission was evaluated according to the European Cooperative Oncology Group score.<sup>11</sup> The grades were defined as follows: grade 0 = fully active, able to carry on all predisease performance without restriction; grade 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; grade 2 = ambulatory and capable of all self-care but unable to carry out any work activity, up and about more than 50% of working hours; grade 3 = capable of only limited self-care, confined to bed or chair more than 50% of working hours; and grade 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair.

The choice of antibiotic regimen was made according to the national guidelines proposed by the Japanese Respiratory Society.<sup>12</sup> The administration of systemic corticosteroids was left to the discretion of each treating pulmonologist. Treatment with early adjunctive systemic corticosteroids was defined as administration of dosages equivalent to prednisone of  $\geq 20$  mg/day, which is considered as a "stress dose" of systemic corticosteroids for pneumonia,<sup>13</sup> added to the initial intravenous antibiotic medication.

The primary endpoint of this study was mortality within 28 days of admission. The secondary endpoints were requirement for intensive care and occurrence of adverse events. Requirement for intensive care was defined as the use of mechanical ventilation or vasopressors against shock. Adverse events were defined as hyperglycemia with requirement for additional glucose-lowering therapy, confusion, nosocomial infection, or gastrointestinal bleeding.

### Statistical analysis

The data were expressed as numbers or medians (25th–75th percentile range). The differences between the two groups

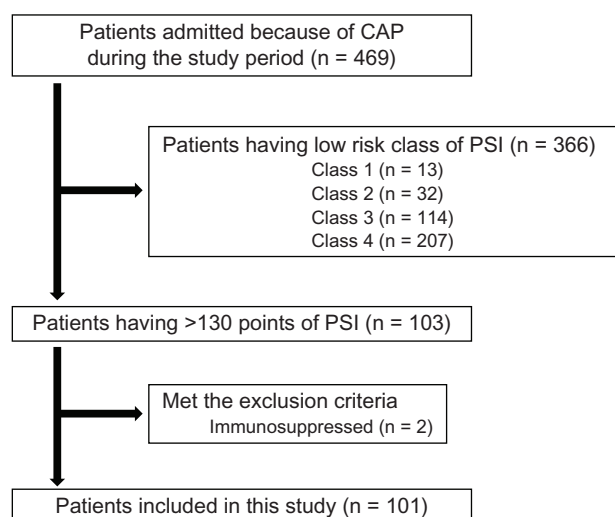
were tested using the nonparametric Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Survival curves from admission were plotted using the Kaplan–Meier method, and the comparison between two curves was performed using the logrank test. To investigate the independent factors associated with mortality, multivariate analysis was performed using the Cox proportional hazard model. The variables incorporated in the multivariate analysis were the factors significantly associated with mortality at the 0.20 level in univariate analysis. The results were expressed as hazard ratio (HR) and 95% confidence interval (CI). A two-tailed probability value <0.05 was considered to be statistically significant.

## Results

### Patient population

During the study period, a total of 469 patients were admitted because of CAP. Of these, 103 had a PSI score of >130 points on admission. Two patients were excluded because of immunosuppression. Thus finally, 101 patients having >130 points of PSI on admission were enrolled in this study (Figure 1).

The baseline characteristics of enrolled patients are shown in Table 1. No one had advanced liver disease, while eight patients (7.9%) had chronic kidney disease. Fourteen patients (13.9%) had underlying lung diseases, including COPD (*n* = 11), bronchial asthma (*n* = 2), and chronic interstitial pneumonia (*n* = 1). Thirty-two patients (31.7%) died within 28 days of admission, and 45 patients (44.6%) needed intensive care. Causative pathogens were detected



**Figure 1** Flow diagram explaining recruitment of study population.  
**Abbreviations:** CAP, community-acquired pneumonia; PSI, pneumonia severity index.

**Table 1** Baseline characteristics of enrolled patients

Characteristics	Values
Number	101
Age, years	86 (81–91)
Male patients	66 (65.3)
From nursing home	57 (56.4)
Performance status	3 (2–3)
Physical findings on admission	
Systolic blood pressure <90 mmHg	22 (21.8)
Altered mental status <sup>†</sup>	53 (52.5)
Requirement for high-flow oxygen <sup>‡</sup>	51 (50.5)
Heart rate, per minute	104 (86–116)
Laboratory findings on admission	
C-reactive protein, mg/dL	12.52 (5.96–23.55)
Leukocyte count, 10 <sup>9</sup> cells/L	11.7 (8.6–14.2)
Blood urea nitrogen, mg/dL	31.8 (21.3–43.3)
Albumin, g/dL	3.1 (2.6–3.5)
Sodium, mEq/L	138 (132–143)
Glucose, mg/dL	133 (109–174)
Creatinine, mg/dL	1.01 (0.66–1.51)
Hematocrit, %	35.4 (30.3–39.2)
pH of arterial blood	7.41 (7.33–7.47)
PaCO <sub>2</sub> , mmHg	41.4 (34.1–48.0)
Radiographic findings on admission	
Bilateral infiltrates	72 (71.3)
Pleural effusion	38 (37.6)
Coexisting illnesses	
Heart failure	25 (24.8)
Diabetes mellitus	16 (15.8)
Cerebrovascular diseases	42 (41.6)
Neoplastic diseases	9 (8.9)
Chronic kidney diseases	8 (7.9)
COPD	11 (10.9)
Other lung diseases	3 (3.0)
Pneumonia severity index	152 (139–179)
Initial antibiotic regimens	
Antipseudomonal beta-lactams	81 (80.2)
Fluoroquinolones	14 (13.9)
Tetracyclines	25 (24.8)
Clindamycin	9 (8.9)
Early adjunctive systemic steroids	30 (29.7)
Clinical outcomes	
Mortality within 28 days of admission	32 (31.7)
Requirement for intensive care	45 (44.6)

**Notes:** Data are expressed as number (%) or median (25th–75th percentile). <sup>†</sup>Defined as a state of awareness that differed from the normal awareness of each person; <sup>‡</sup>defined as a necessity of oxygen inhalation with mask or mechanical ventilation in order to keep arterial oxygen saturation  $\geq$ 90%.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood.

in 56 patients (55.4%) and are listed in Table 2. The most frequently detected pathogen was *S. pneumoniae* (*n* = 17, 16.8%).

### Indication for and impact of early adjunctive systemic corticosteroids

Thirty patients (29.7%) were administered systemic corticosteroids added to their initial antibiotic medication.

**Table 2** Detected pathogens

Microorganism	Number
<i>Streptococcus pneumoniae</i>	17 (16.8)
<i>Klebsiella pneumoniae</i>	9 (8.9)
MRSA	9 (8.9)
<i>Staphylococcus</i> spp.	8 (7.9)
<i>Pseudomonas aeruginosa</i>	6 (5.9)
<i>Escherichia coli</i>	2 (2.0)
<i>Proteus mirabilis</i>	2 (2.0)
<i>Acinetobacter baumannii</i>	1 (1.0)
<i>Enterococcus</i> spp.	1 (1.0)
<i>Serratia marcescens</i>	1 (1.0)
Unknown	45 (44.6)

**Note:** Data are expressed as number (%).

**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

The dosages of adjunctive systemic corticosteroids are listed in Table 3. The median dosage of early adjunctive systemic corticosteroids was 50 mg/day (30–50 mg/day) of an equivalent to prednisone. Most patients treated with early adjunctive systemic corticosteroids received a bolus intravenous infusion for a period shorter than 8 days.

The characteristics of patients treated with and without early adjunctive systemic corticosteroids are shown in Table 4. Of physical findings on admission, the patients treated with early adjunctive systemic corticosteroids were more likely to have an alteration of mental status (80.0% versus 40.8%) ( $P < 0.001$ ) and requirement for high flow oxygen inhalation (66.7% versus 43.7%) ( $P = 0.049$ ) than were those without early corticosteroids. Of laboratory findings, the patients treated with early adjunctive systemic corticosteroids were more likely to have lower leukocyte counts ( $10.4 \times 10^9$  cells/L versus  $12.1 \times 10^9$  cells/L) ( $P = 0.039$ ), lower sodium levels (137 mEq/L versus 139 mEq/L) ( $P = 0.031$ ), and higher

**Table 3** Dosage and duration of early systemic corticosteroids

	Number
Corticosteroids	
Methylprednisolone	17
Prednisolone	12
Dexamethasone	1
Dosage (equivalent to prednisone)	
20–60 mg/day	25
$\geq 61$ mg/day	5
Dosing duration	
3 days	6
4–7 days	18
$\geq 8$ days	6
Dosing methods	
Orally	0
Intravenously	30
Bolus infusion	29
Continuous infusion	1

albumin levels (3.3 g/dL versus 3.0 g/dL) ( $P = 0.003$ ). Of coexisting illnesses, the patients treated with early adjunctive systemic corticosteroids were more likely to have COPD (26.7% versus 4.2%) ( $P = 0.002$ ) and other lung diseases (10.0% versus 0) ( $P = 0.024$ ) and less likely to have cerebrovascular diseases (23.3% versus 49.3%) ( $P = 0.017$ ). Of initial antibiotic regimens, the patients treated with early adjunctive systemic corticosteroids were more likely to receive fluoroquinolones (26.7% versus 8.5%) ( $P = 0.025$ ). Of radiographic and microbiological findings, no significant differences were observed between the patients with and without early adjunctive systemic corticosteroids.

Concerning the clinical outcomes, mortality and the requirement for intensive care did not differ significantly between the patients treated with and without early adjunctive systemic corticosteroids.

## Adverse events

The adverse events of patients treated with and without early adjunctive systemic corticosteroids are shown in Table 5. There were no significant differences of any adverse event between the groups. Septic shock induced by urinary tract infection occurred in one patient treated without early corticosteroids after 15 days of admission, while the other nosocomial infections were recurrence of pneumonia. Fatal gastrointestinal bleeding occurred in one patient treated without early corticosteroids after 10 days of admission.

## Factors associated with mortality

A comparison of the characteristics of deceased and surviving patients is shown in Table 6. The deceased patients were more likely to have needed intensive care (78.1% versus 29.0%) ( $P < 0.001$ ) than were the surviving patients. Of laboratory findings, the deceased patients were more likely to have higher CRP levels (18.78 mg/dL versus 10.79 mg/dL) ( $P = 0.017$ ), higher blood urea nitrogen levels (39.8 mg/dL versus 31.0 mg/dL) ( $P = 0.016$ ), and lower albumin levels (2.9 g/dL versus 3.2 g/dL) ( $P = 0.005$ ). Of microbiological findings, the deceased patients were more likely to have an etiology of methicillin-resistant *Staphylococcus aureus* (18.8% versus 4.3%) ( $P = 0.027$ ). Of initial antibiotic regimens, the deceased patients were more likely to receive antipseudomonal beta-lactam agents (93.8% versus 73.9%) ( $P = 0.03$ ). Of physical findings, radiographic findings, and coexisting illnesses, no significant differences were observed between the deceased and surviving patients.

**Table 4** Characteristics between patients with and without early systemic steroids

	Early systemic steroids	Without early steroids	P-value
Number	30	71	
Age, years	85 (80–90)	86 (81–92)	0.517
Male patients	22 (73.3)	44 (62.0)	0.361
From nursing home	13 (43.3)	44 (62.0)	0.124
Performance status	3 (1–3)	3 (2–3)	0.495
Physical findings on admission			
Systolic blood pressure <90 mmHg	10 (33.3)	12 (16.9)	0.111
Altered mental status <sup>†</sup>	24 (80.0)	29 (40.8)	<0.001
Requirement for high-flow oxygen <sup>‡</sup>	20 (66.7)	31 (43.7)	0.049
Heart rate, per minute	111 (95–123)	100 (83–113)	0.096
Laboratory findings on admission			
C-reactive protein, mg/dL	11.65 (5.16–23.18)	13.16 (6.24–23.46)	0.815
Leukocyte count, 10 <sup>9</sup> cells/L	10.4 (6.4–12.7)	12.1 (9.4–16.8)	0.039
Blood urea nitrogen, mg/dL	32.8 (25.8–40.7)	31.5 (18.9–43.8)	0.499
Albumin, g/dL	3.3 (3.1–3.7)	3.0 (2.6–3.4)	0.003
Sodium, mEq/L	137 (129–140)	139 (134–145)	0.031
Glucose, mg/dL	142 (116–155)	132 (106–178)	0.864
Creatinine, mg/dL	1.06 (0.75–1.91)	0.96 (0.63–1.38)	0.276
Hematocrit, %	37.1 (32.7–40.4)	35.1 (29.3–38.7)	0.089
pH of arterial blood	7.37 (7.29–7.46)	7.43 (7.34–7.48)	0.126
PaCO <sub>2</sub> , mmHg	39.4 (33.9–48.2)	41.7 (34.3–47.8)	0.854
Radiographic findings on admission			
Bilateral infiltrates	24 (80.0)	48 (67.6)	0.238
Pleural effusion	9 (30.0)	29 (40.8)	0.372
Coexisting illnesses			
Heart failure	6 (20.0)	19 (26.8)	0.616
Diabetes mellitus	6 (20.0)	10 (14.1)	0.552
Cerebrovascular diseases	7 (23.3)	35 (49.3)	0.017
Neoplastic diseases	2 (6.7)	7 (9.9)	0.722
Chronic kidney diseases	2 (6.7)	6 (8.5)	>0.999
COPD	8 (26.7)	3 (4.2)	0.002
Other lung diseases	3 (10.0)	0	0.024
Pneumonia severity index	149 (141–179)	154 (135–175)	0.629
Identification of pathogens			
<i>Streptococcus pneumoniae</i>	7 (23.3)	10 (14.1)	0.26
<i>Klebsiella pneumoniae</i>	5 (16.7)	4 (5.6)	0.121
MRSA	3 (10.0)	6 (8.5)	>0.999
Initial antibiotic regimens			
Antipseudomonal beta-lactams	24 (80.0)	57 (80.3)	>0.999
Fluoroquinolones	8 (26.7)	6 (8.5)	0.025
Tetracyclines	8 (26.7)	17 (23.9)	0.804
Clindamycin	1 (3.3)	8 (11.3)	0.274
Clinical outcomes			
Mortality within 28 days of admission	6 (20.0)	26 (36.6)	0.159
Requirement for intensive care	16 (53.3)	29 (40.8)	0.279

**Notes:** Data are expressed as number (%) or median (25th–75th percentile). <sup>†</sup>Defined as a state of awareness that differed from the normal awareness of each person; <sup>‡</sup>defined as a necessity of oxygen inhalation with mask or mechanical ventilation in order to keep arterial oxygen saturation  $\geq 90\%$ .

**Abbreviations:** COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood.

The Kaplan–Meier survival curves for mortality within 28 days of admission did not differ significantly between the patients treated with and without early adjunctive systemic corticosteroids ( $P = 0.098$ ) (Figure 2).

The results of multivariate analysis for mortality are shown in Table 7. Factors independently associated

with mortality were blood urea nitrogen (HR 1.02, 95% CI 1.00–1.04) ( $P = 0.013$ ), serum albumin level (HR 0.44, 95% CI 0.22–0.86) ( $P = 0.017$ ), a requirement for intensive care (HR 4.93, 95% CI 1.75–13.87) ( $P = 0.003$ ), and the therapy with early adjunctive systemic corticosteroids (HR 0.29, 95% CI 0.11–0.81) ( $P = 0.018$ ).

**Table 5** Adverse events between patients with and without early systemic corticosteroids

	Early systemic steroids (n = 30)	Without early steroids (n = 71)	P-value
Hyperglycemia with additional intervention	2 (6.7)	5 (7.0)	>0.999
Confusion	6 (20.0)	6 (8.5)	0.174
Nosocomial infection	2 (6.7)	5 (7.0)	>0.999
Gastrointestinal bleeding	0	2 (2.8)	>0.999

**Note:** Data are expressed as number (%).

## Discussion

The present study in very severe CAP showed that (1) the addition of systemic corticosteroids to initial antibiotics was more frequently observed in patients having alteration of mental status, serious respiratory failure or underlying lung diseases, and receiving fluoroquinolones as initial antibiotics; (2) the dosage of additional (to initial antibiotics) systemic corticosteroids was less than 60 mg/day of an equivalent to prednisone by bolus intravenous infusion for a period shorter than 8 days in most patients; (3) the occurrence of adverse events did not differ between the patients treated with and without early adjunctive systemic corticosteroids; and (4) the early adjunctive systemic corticosteroid was an independent protective factor for mortality.

Systemic inflammatory responses brought about by severe pneumonia cause critical conditions, such as respiratory failure and hypotension.<sup>14,15</sup> Corticosteroids inhibit the expression and action of many cytokines involved in inflammatory responses by binding to their specific receptors, which are located in the cytoplasm of nearly all human cells.<sup>16</sup> Therefore, systemic corticosteroids can suppress inflammatory responses in specific tissues as well as in the whole body. However, not many CAP studies have shown that adjunctive systemic corticosteroids reduce the risk of mortality.<sup>6–9,17</sup> A recent meta-analysis showed that the addition of systemic corticosteroids for treatment of pneumonia accelerated the resolution of symptoms but did not reduce the mortality.<sup>18</sup> To our knowledge, only two CAP studies have shown the efficacy of systemic corticosteroids for reducing mortality.<sup>5,19</sup> In order to assess the influence of adjunctive systemic corticosteroids on mortality, it is necessary to study critically ill CAP patients. In fact, in clinical practice, the administration of adjunctive systemic corticosteroids is taken into consideration for critically ill CAP patients. However, most of the earlier CAP studies included patients with a mild to moderate

severity of illness. In the present study, we confined our study cohort to critically ill patients, as per PSI, which is regarded as a reliable severity indicator of CAP throughout the world.<sup>20–22</sup> This may be one of the reasons why our study showed favorable efficacy of systemic corticosteroids in reducing the risk of mortality in CAP patients.

It is not clear whether continuous or bolus infusion of corticosteroids is more appropriate for critically ill patients. Confalonieri et al<sup>19</sup> reported that the continuous infusion of hydrocortisone for severe CAP contributed to favorable clinical outcomes.<sup>19</sup> In contrast, Mikami et al showed that the bolus infusion of prednisolone for moderate to severe CAP contributed to prompt resolution of clinical symptoms.<sup>9</sup> In patients with septic shock, a prospective, randomized study produced by Loisa et al has shown that there were no differences in mortality and vasopressor requirements of patients treated with continuous corticosteroid infusion and those treated with bolus infusion.<sup>23</sup> Similarly, a randomized double-blinded trial on ulcerative colitis showed that continuous corticosteroid infusion was not superior to bolus infusion in terms of efficacy and safety.<sup>24</sup> In the present study, systemic corticosteroids were administered by bolus infusion to all patients except one. Our study may suggest that the bolus infusion of corticosteroids is appropriate for treating critically ill patients.

Systemic corticosteroids have several undesirable clinical effects, such as immunosuppression, hyperglycemia, and changes of mental condition. These adverse events often make patient care difficult.<sup>25–27</sup> Nevertheless, there are few reports showing severe complications associated with adjunctive systemic corticosteroids in patients with CAP. In their CAP study, Meijvis et al documented that hyperglycemia was more common in patients treated with dexamethasone therapy than in those treated without dexamethasone, but the requirement for additional glucose-lowering therapy did not differ between the groups.<sup>8</sup> Similarly, in the present CAP study, the early adjunctive systemic corticosteroids did not bring more adverse events compared with the therapy without early corticosteroids. It is well known that the incidence of significant side effects caused by systemic corticosteroids increases with the dose and duration of administration.<sup>28</sup> Low-dose and short-term systemic corticosteroids are administered in most patients with CAP, including the patients in the present study. This type of treatment can be associated with safety of adjunctive systemic corticosteroids in patients with CAP.

We should mention that our current study has several limitations. First, our present study was not a placebo-controlled

**Table 6** Characteristics between deceased and surviving patients

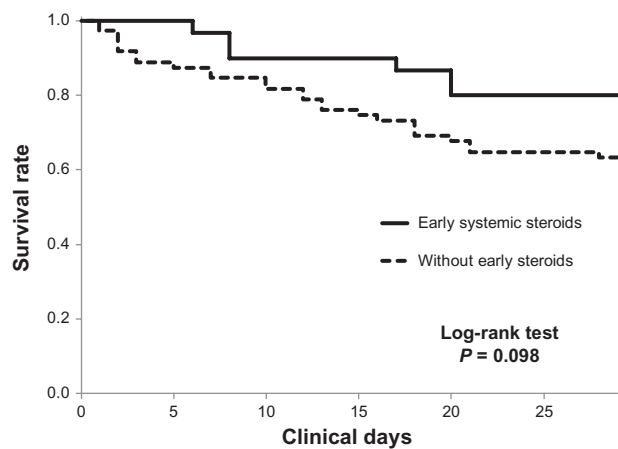
	Deceased	Surviving	P-value
Number	32	69	
Age, years	84 (79–89)	86 (82–92)	0.449
Male patients	21 (65.6)	45 (65.2)	>0.999
From nursing home	18 (56.3)	39 (56.5)	>0.999
Performance status	3 (2–3)	3 (2–3)	0.647
Physical findings on admission			
Systolic blood pressure <90 mmHg	7 (21.9)	15 (21.7)	>0.999
Altered mental status <sup>†</sup>	20 (62.5)	33 (47.8)	0.202
Requirement for high-flow oxygen <sup>‡</sup>	20 (62.5)	31 (44.9)	0.135
Heart rate, per minute	105 (94–119)	104 (84–116)	0.571
Laboratory findings on admission			
C-reactive protein, mg/dL	18.78 (8.60–26.55)	10.79 (4.29–19.86)	0.017
Leukocyte count, 10 <sup>9</sup> cells/L	10.3 (8.7–14.2)	11.9 (8.3–14.2)	0.748
Blood urea nitrogen, mg/dL	39.8 (24.5–69.1)	31.0 (21.3–40.0)	0.016
Albumin, g/dL	2.9 (2.2–3.2)	3.2 (2.8–3.6)	0.005
Sodium, mEq/L	140 (133–148)	138 (132–141)	0.168
Glucose, mg/dL	118 (104–171)	138 (110–174)	0.184
Creatinine, mg/dL	1.19 (0.69–2.04)	0.96 (0.62–1.30)	0.161
Hematocrit, %	36.0 (29.5–38.9)	35.1 (30.5–39.5)	0.884
pH of arterial blood	7.36 (7.33–7.46)	7.43 (7.33–7.45)	0.25
PaCO <sub>2</sub> , mmHg	42.0 (35.6–49.9)	41.4 (33.2–48.0)	0.531
Radiographic findings on admission			
Bilateral infiltrates	26 (81.3)	46 (66.7)	0.16
Pleural effusion	12 (37.5)	26 (37.7)	>0.999
Coexisting illnesses			
Heart failure	7 (21.9)	18 (26.1)	0.805
Diabetes mellitus	6 (18.8)	10 (14.5)	0.572
Cerebrovascular diseases	12 (37.5)	30 (43.5)	0.666
Neoplastic diseases	2 (6.3)	7 (10.1)	0.715
Chronic kidney diseases	3 (9.4)	5 (7.2)	0.706
COPD	3 (9.4)	8 (11.6)	>0.999
Other lung diseases	1 (3.1)	2 (2.9)	>0.999
Pneumonia severity index	163 (147–180)	146 (136–171)	0.071
Identification of pathogens			
<i>Streptococcus pneumoniae</i>	4 (12.5)	13 (18.8)	0.571
<i>Klebsiella pneumoniae</i>	1 (3.1)	8 (11.6)	0.266
MRSA	6 (18.8)	3 (4.3)	0.027
Initial antibiotic regimens			
Antipseudomonal beta-lactams	30 (93.8)	51 (73.9)	0.03
Fluoroquinolones	3 (9.4)	11 (15.9)	0.539
Tetracyclines	9 (28.1)	16 (23.2)	0.625
Clindamycin	2 (6.3)	7 (10.1)	0.715
Early adjunctive systemic steroids	6 (18.8)	24 (34.8)	0.159
Requirement for intensive care	25 (78.1)	20 (29.0)	<0.001

**Notes:** Data are expressed as number (%) or median (25th–75th percentile). <sup>†</sup>Defined as a state of awareness that differed from the normal awareness of each person; <sup>‡</sup>defined as a necessity of oxygen inhalation with mask or mechanical ventilation in order to keep arterial oxygen saturation  $\geq 90\%$ .

**Abbreviations:** COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood.

interventional study. Therefore, the dosage and term of systemic corticosteroids and the antibiotic regimen varied for each patient. However, most of our study cohort received low-dose and short-term systemic corticosteroids, in the same way as in former interventional CAP studies. Additionally, in order to reduce the influence of various confounders as much as possible, we performed the

multivariate analysis for assessment of the factors associated with mortality. Second, this study cohort included a limited number of patients because it was a single-center observational study. To demonstrate the clinical impact of early adjunctive systemic corticosteroids for very severe CAP, further multicenter studies including a large number of patients with very severe CAP are needed. Third, adrenocortical function



**Figure 2** Kaplan–Meier survival curves in patients treated with and without early adjunctive systemic corticosteroids. No significant difference was observed between both groups ( $P = 0.098$ ).

was not evaluated in our study. Although some former studies have shown that relative adrenal insufficiency has little influence on the clinical courses of CAP,<sup>9,29,30</sup> we could not exclude the possibility that adjunctive systemic corticosteroids compensated for adrenal insufficiency. Finally, most patients in our study cohort were of advanced age. Therefore, the mortality rate in our present study may have been higher than that in other CAP studies. Although the age did not differ between deceased and surviving patients in our present study, additional studies including critically ill younger patients are

**Table 7** Multivariate analysis for mortality within 28 days of admission

	Hazard ratio (95% CI)	P-value
Physical findings on admission		
Requirement for high-flow oxygen <sup>‡</sup>	1.95 (0.63–6.01)	0.246
Laboratory findings on admission		
C-reactive protein	0.99 (0.96–1.03)	0.69
Blood urea nitrogen	1.02 (1.00–1.04)	0.013
Albumin	0.44 (0.22–0.86)	0.017
Sodium	0.99 (0.95–1.02)	0.44
Glucose	0.99 (0.99–1.00)	0.053
Creatinine	0.89 (0.58–1.36)	0.578
Radiographic findings on admission		
Bilateral infiltrates	1.55 (0.48–5.05)	0.466
Pneumonia severity index	1.00 (0.98–1.02)	0.899
Identification of pathogens		
MRSA	2.92 (0.72–11.83)	0.133
Initial antibiotic regimens		
Antipseudomonal beta-lactams	1.39 (0.30–6.46)	0.674
Early adjunctive systemic steroids	0.29 (0.11–0.81)	0.018
Requirement for intensive care	4.93 (1.75–13.87)	0.003

**Note:** <sup>‡</sup>Defined as a necessity of oxygen inhalation with mask or mechanical ventilation in order to keep arterial oxygen saturation  $\geq 90\%$ .

**Abbreviations:** CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*.

needed in order to prove the clinical impact of early adjunctive systemic corticosteroids for very severe CAP.

In conclusion, early adjunctive systemic corticosteroids may be expected to have the efficacy to reduce the mortality in very severe CAP. We can consider the administration of systemic corticosteroids simultaneously with initial antibiotic medication in cases of very severe CAP, although a larger-scale prospective study is necessary.

## Author contributions

All authors contributed to the conception of the study and the data collection, and critically reviewed the manuscript. Dr Ugajin additionally performed the data analysis and wrote the manuscript, and Dr Yamaki also proofread the manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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