Clinical characteristics and risk factors for mortality in patients with community-acquired staphylococcal pneumonia

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ABSTRACT

Staphylococcus aureus (\(S.\) aureus) is increasing in prevalence as a causative pathogen of community-acquired pneumonia (CAP). However, reports on the clinical features and mortality risk factors for \(S.\) aureus CAP are limited. We therefore aimed to identify the clinical characteristics and risk factors for mortality in these patients. We performed a post hoc and multivariate analysis of a multicenter prospective observational study that included adult hospitalized patients with \(S.\) aureus CAP. To elucidate the features of \(S.\) aureus CAP, we comparatively analyzed pneumococcal CAP (PCAP). We analyzed 196 patients with \(S.\) aureus CAP and 198 patients with PCAP. \(S.\) aureus CAP had a 30-day mortality of 16\% (31/196) and a higher frequency of factors such as advanced age, comorbidities, poor functional ability, altered mental status, hypoalbuminemia, hyponatremia/hypernatremia, acidemia, and hypoxemia. In the multivariate analysis, the significant risk factors for mortality in \(S.\) aureus CAP were \(\text{PaO}_2/\text{FiO}_2 \leq 250\) [adjusted odds ratio (AOR), 3.29; 95\% confidence interval (CI), 1.20–9.04] and albumin <3.0 g/dL (AOR, 2.41; 95\% CI, 1.01–5.83). Non-ambulatory status tended to increase the risk (AOR, 2.40; 95\% CI, 0.93–6.17). Methicillin resistance was not associated with mortality. In PCAP, hypoalbuminemia and non-ambulatory status affected mortality but hypoxemia did not. In conclusion, patients with \(S.\) aureus CAP have distinct clinical features, and their mortality risk factors can include hypoxemia and hypoalbuminemia. Physicians should recognize that the factors influencing mortality might differ somewhat among causative pathogens, and appropriate management should be performed after obtaining information on the causative pathogen.

Keywords: Staphylococcus aureus, community-acquired pneumonia, pneumococcal pneumonia, clinical characteristics, mortality

Abbreviations:
\(S.\) aureus: Staphylococcus aureus
CAP: community-acquired pneumonia
INTRODUCTION

Pneumonia is one of the leading causes of death worldwide.\(^1\) \textit{Staphylococcus aureus} (\textit{S. aureus}), one of the causative pathogens of community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP), is increasing in prevalence.\(^2\) Several reports have shown the emergence of \textit{S. aureus} CAP as one of the causes of severe pneumonia leading to critical illness and death.\(^3-7\) To provide better management practices for patients with \textit{S. aureus} CAP, their clinical characteristics and factors contributing to mortality should be clarified.

The initial step in managing patients with CAP is to assess pneumonia severity to determine site-of-care. In recent decades, scoring systems have been developed such as the Pneumonia Severity Index (PSI) and CURB-65 [confusion, blood urea nitrogen (BUN) > 7 mmol/L (20 mg/dL), respiratory rate ≥ 30 bpm, low blood pressure (BP) (diastolic BP ≤ 60 mm Hg or systolic BP < 90 mm Hg), and age ≥ 65 years].\(^8,9\) These scoring systems help physicians distinguish patients with CAP at low mortality risk from those at high risk at the diagnosis of pneumonia. However, these scoring systems consist of findings observed at diagnosis, and the microbiological test results usually obtained after diagnosis are not included in the systems. Furthermore, the microbial etiology of CAP has been demonstrated to be a mortality risk factor.\(^10\) Thus, the types and weight of risk factors for adverse outcomes might differ among patients with CAP according to the causative organisms. Studies on patients with pneumococcal pneumonia have revealed various prognostic factors.\(^11,12\)

However, studies to date on the risk factors for poor outcomes in \textit{S. aureus} CAP have been scarce and have focused on identifying the microbial risk factors for poor outcomes, especially in methicillin-resistant \textit{Staphylococcus aureus} (MRSA), such as the Panton-Valentine leukocidin (PVL) gene, the toxic shock syndrome toxin-1 (TSST-1) gene, arginine dysfunction, and Staphylococcal Cassette Chromosome \textit{mec} (SCC\textit{mec}) types.\(^13,14\) To our knowledge, host factors for mortality in \textit{S. aureus} CAP have not been clarified. We therefore designed this post hoc analysis study to investigate the clinical characteristics and mortality risk factors for \textit{S. aureus} CAP using a dataset from a prospective multicenter observational study.
PATIENTS AND METHODS

Study design and setting
This study employed prospectively collected data from an observational multicenter study of patients with pneumonia, which was conducted from March 15 to December 22, 2010 at 10 medical institutions in Japan that were members of the Central Japan Lung Study Group. This study was approved by the institutional review boards of the medical institutions. The study protocol adhered to the Japanese Ethical Guidelines for Epidemiological Studies. Although informed consent was not required from the study participants, the study information was disclosed to the target patients through the Internet, brochures, and bulletin boards at the participating institutions to give the candidates the opportunity to decline participation. This study was registered with the University Medical Information Network in Japan (number UMIN000003306).

Patients
All adult patients (aged ≥ 20 years) hospitalized with CAP or HCAP were enrolled. The definitions of pneumonia, CAP, and HCAP followed the international guidelines. S. aureus CAP was defined as the detection of S. aureus in cultures from sputum samples, tracheobronchial aspirates, bronchoalveolar lavage fluid, pleural fluid, and blood. The S. aureus CAP group included MRSA and methicillin-susceptible Staphylococcus aureus (MSSA). Pneumococcal CAP was defined when S. pneumoniae was detected in the cultures from the samples mentioned above. Patients in whom S. pneumoniae and other pathogens were co-detected were not included in the pneumococcal CAP group. Patients with co-detection of S. aureus and S. pneumoniae were included in the S. aureus CAP group. Details on the inclusion and exclusion criteria are described elsewhere.

Procedure and data collection
Details on the definition of variables, procedures, data collection, and micro bacteriological assessment in the prospective study were described previously. Antibiotic treatment was classified as appropriate initial antibiotics when identified pathogens were susceptible to the initially prescribed antibiotics.

Endpoint
The primary endpoint in this study was 30-day all-cause mortality, which was defined as death within 30 days of the pneumonia diagnosis.

Statistical analysis
We performed statistical analyses with SPSS (version 25). All tests were two-tailed, and a p-value < 0.05 was considered significant. We employed Pearson’s chi-squared test or the Mantel extension test for trends in the analysis of discrete variables. For the analysis of risk factors for 30-day mortality in S. aureus CAP, we performed univariable and multivariate analyses. The univariate analysis employed the following variables: sex, age, comorbidities, non-ambulatory status, physical findings, laboratory findings and radiographic findings, variables decided a priori by referring to previous reports. When determining the cutoff values of the continuous variables, we considered the values from previous studies and performed histograms for each variable in this study.

We performed a multivariate logistic regression analysis using a forced entry selection method with variables that had significant p-value in the univariate analysis (p ≤ 0.05) in addition to the following variables: age, sex, and presence of methicillin resistance. We calculated the adjusted odds ratios (AORs) and corresponding 95% confidence intervals (CIs).
Subgroup analyses of the patients with pneumococcal pneumonia were performed to compare the risk and risk factors for 30-day mortality between the *S. aureus* and pneumococcal CAP groups.

**RESULTS**

**Patient flow and characteristics**

In total, 1413 of the 1742 assessed patients with pneumonia were identified as eligible, 526 of whom had HCAP. Of the eligible patients, 196 (14%) were identified with *S. aureus* CAP, and 198 had pneumococcal CAP (14%). The *S. aureus* CAP group included 119 patients (61%) with MSSA and 77 patients (39%) with MRSA and had a 30-day mortality of 16% (31 deaths) (Figure 1). Table 1 shows the characteristics of the two CAP groups; the pneumococcal CAP patients are shown as a reference. Certain clinical characteristics were more prevalent in the *S. aureus* CAP group, including age ≥ 80 years, central nervous system (CNS) disorder, non-ambulatory
Predictors of mortality in S. aureus CAP

status, Glasgow Coma Scale (GCS) ≤ 12, albumin < 3.0 g/dL, sodium levels < 130 or ≥ 150 mEq/L, pH < 7.35, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO\textsubscript{2}/FiO\textsubscript{2}) ≤ 250, and bilateral lung involvement. Eighty-eight percent of the S. aureus CAP group were classified into more severe PSI classes (IV and V).

| Variables | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------|--------------------|-------------------------------|------------------------|
| Age ≥80 years | 572 (40.5) | 91 (46.4) | 62 (31.3) |
| Sex, male | 915 (64.8) | 124 (63.3) | 122 (61.6) |

Comorbidities

| Variables                               | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------------------------------------|--------------------|-------------------------------|------------------------|
| Neoplastic diseases                     | 208 (14.7)         | 27 (13.8)                      | 24 (12.1)              |
| Chronic lung diseases                   | 470 (33.3)         | 71 (36.2)                      | 53 (26.8)              |
| Congestive heart failure                | 183 (13.0)         | 32 (16.3)                      | 15 (7.6)               |
| Chronic renal diseases                  | 113 (8.0)          | 14 (7.1)                       | 15 (7.6)               |
| Chronic liver diseases                  | 53 (3.8)           | 6 (3.1)                        | 8 (4.0)                |
| Central nervous system disorders        | 304 (21.5)         | 64 (32.7)                      | 25 (12.6)              |
| Diabetes                                | 258 (18.3)         | 31 (15.8)                      | 35 (17.7)              |
| Immunosuppression                       | 129 (9.1)          | 14 (7.1)                       | 22 (11.1)              |
| Non-ambulatory status                   | 338 (23.9)         | 82 (41.8)                      | 35 (17.7)              |

Physical findings

| Variables                               | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------------------------------------|--------------------|-------------------------------|------------------------|
| Glasgow Coma Scale ≤12                  | 249 (17.6)         | 61 (31.1)                      | 21 (10.6)              |
| Pulse rate ≥125 beats per min           | 140 (9.9)          | 24 (12.2)                      | 20 (10.1)              |
| Systolic blood pressure <90 mm Hg       | 81 (5.5)           | 22 (11.2)                      | 14 (7.1)               |
| Respiration rate ≥30 breaths per min    | 314 (22.2)         | 48 (24.5)                      | 43 (21.7)              |

Laboratory findings

| Variables                               | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------------------------------------|--------------------|-------------------------------|------------------------|
| Hematocrit <0.3                         | 213 (15.1)         | 33 (16.8)                      | 24 (12.1)              |
| Platelet count <120,000/mm\textsuperscript{3} | 115 (8.1)         | 18 (9.2)                       | 14 (7.1)               |
| Albumin <3.0 g/dL                       | 478 (33.8)         | 96 (49.0)                      | 57 (28.8)              |
| Glucose ≤60 or ≥300 mg/dL               | 69 (4.9)           | 14 (7.1)                       | 11 (5.6)               |
| Blood urea nitrogen ≥30 mg/dL           | 310 (21.9)         | 56 (28.6)                      | 44 (22.2)              |
| Na <130 or ≥150 mEq/L                   | 118 (8.4)          | 28 (14.3)                      | 14 (7.1)               |
| Creatinine ≥1.2                         | 290 (20.5)         | 36 (18.4)                      | 43 (21.7)              |
| pH <7.35                                | 149 (10.5)         | 27 (13.8)                      | 14 (7.1)               |
| PaO\textsubscript{2}/FiO\textsubscript{2} ≤250 | 531 (37.6)         | 104 (53.1)                     | 63 (31.8)              |

Radiographic findings

| Variables                               | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------------------------------------|--------------------|-------------------------------|------------------------|
| Bilateral lung involvement              | 649 (45.9)         | 110 (56.1)                     | 84 (42.4)              |
| Pleural effusion                        | 344 (24.3)         | 53 (27.0)                      | 37 (18.7)              |

Pneumonia Severity Index class

| Variables                               | All CAP (n = 1413) | Staphylococcus aureus (n = 196) | Pneumococcus (n = 198) |
|-----------------------------------------|--------------------|-------------------------------|------------------------|
| I–III                                   | 441 (31.2)         | 35 (17.9)                      | 81 (40.9)              |
| IV                                      | 534 (37.8)         | 86 (43.9)                      | 74 (37.4)              |
| V                                       | 372 (26.3)         | 67 (34.2)                      | 37 (18.7)              |
CAP: community-acquired pneumonia  
PaO₂/FiO₂: ratio of arterial oxygen partial pressure to fractional inspired oxygen  
Data are present as number and percentage.  
Immunosuppression included any immunosuppressive diseases such as congenital and acquired immunodeficiency, hematological diseases, and neutropenia (<1000/mm³); treatment with immunosuppressive drugs within the previous 30 days; and corticosteroids dosages of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.  
Non-ambulatory status was defined as being bedridden or using a wheelchair because of difficulty walking.

Table 2 lists the characteristics of the survivors and non-survivors in the S. aureus CAP group. Many of the patients who died had the following physical and laboratory findings: non-ambulatory status (68%), GCS ≤ 12 (52%), albumin <3.0 g/dL (65%), pH < 7.35 (26%) and PaO₂/FiO₂ ≤ 250 (81%) (Table 2).

| Variables                          | Survivors (n = 165) | Non-survivors (n = 31) | P value |
|-----------------------------------|---------------------|------------------------|---------|
| Age ≥80 years                     | 75 (45.5)           | 16 (51.6)              | 0.528   |
| Sex, male                         | 105 (63.6)          | 19 (61.3)              | 0.804   |
| Comorbidities                     |                     |                        |         |
| Neoplastic diseases               | 22 (13.3)           | 5 (16.1)               | 0.776   |
| Chronic lung diseases             | 54 (32.7)           | 17 (54.8)              | 0.263   |
| Congestive heart failure          | 26 (15.8)           | 6 (19.4)               | 0.602   |
| Chronic renal diseases            | 12 (7.3)            | 2 (6.5)                | 0.999   |
| Chronic liver diseases            | 5 (3.0)             | 1 (3.2)                | 0.999   |
| Central nervous system disorders  | 52 (31.5)           | 12 (38.7)              | 0.433   |
| Diabetes                          | 27 (16.4)           | 4 (12.9)               | 0.791   |
| Immunosuppression                 | 11 (6.7)            | 3 (9.7)                | 0.468   |
| Non-ambulatory status             | 61 (37.0)           | 21 (67.7)              | 0.001   |
| Physical findings                 |                     |                        |         |
| Glasgow Coma Scale ≤12            | 45 (27.3)           | 16 (51.6)              | 0.007   |
| Pulse rate ≥125 beats per min     | 19 (11.5)           | 5 (16.1)               | 0.549   |
| Systolic blood pressure <90 mm Hg | 17 (10.3)           | 5 (16.1)               | 0.355   |
| Respiration rate ≥30 breaths per min | 36 (21.8)      | 12 (38.7)              | 0.072   |
| Laboratory findings               |                     |                        |         |
| Hematocrit <0.3                   | 28 (17.0)           | 5 (16.1)               | 0.999   |
| Platelet count <120,000/mm³       | 14 (8.5)            | 4 (12.9)               | 0.495   |
| Albumin <3.0 g/dL                 | 76 (46.1)           | 20 (64.5)              | 0.015   |
| Glucose ≤60 or ≥300 mg/dL         | 10 (6.1)            | 4 (12.9)               | 0.244   |
| Blood urea nitrogen ≥30 mg/dL     | 43 (26.1)           | 13 (41.9)              | 0.073   |
| Na <130 or ≥150 mEq/L             | 21 (12.7)           | 7 (22.6)               | 0.164   |
Predictors of mortality in *S. aureus* CAP

| Predictor                        | Total (n=196) | Survivors (n=165) | Non-survivors (n=31) |
|----------------------------------|---------------|-------------------|----------------------|
| Creatinine ≥1.2                  | 30 (18.2)     | 6 (19.4)          | 0.806                |
| pH <7.35                         | 19 (11.5)     | 8 (25.8)          | 0.046                |
| PaO2/FiO2 ≤250                   | 79 (47.9)     | 25 (80.7)         | 0.001                |
| Radiographic findings            |               |                   |                      |
| Bilateral lung involvement       | 90 (54.6)     | 20 (64.5)         | 0.305                |
| Pleural effusion                 | 43 (26.1)     | 10 (32.3)         | 0.476                |
| Pneumonia Severity Index class   |               |                   | 0.013                |
| I–III                            | 34 (20.6)     | 1 (3.2)           |                      |
| IV                               | 73 (44.2)     | 13 (41.9)         |                      |
| V                                | 50 (30.3)     | 17 (54.8)         |                      |

PaO2/FiO2: ratio of arterial oxygen partial pressure to fractional inspired oxygen

**Microbiological findings and appropriateness of antibiotics**

Table 3 presents the microbiological findings of the survivors and non-survivors. In *S. aureus* CAP, we identified a high rate of co-infection (approximately 72%, n=142), especially Gram-negative pathogens, which were detected in 99 patients (51%). The 30-day mortality rates were 21% (16/77) for the patients with MRSA and 13% (19/142) for those with *S. aureus* and other co-infected pathogens, respectively. The most detected Gram-negative pathogens were *Klebsiella pneumoniae*, followed by *Pseudomonas aeruginosa* and *Haemophilus influenzae*. In contrast, we identified Gram-positive pathogen co-infections in only 43 patients (22%). In this study, only one patient with *S. aureus* CAP was identified as co-infected with the influenza virus.

**Table 3** Microbiological findings in the staphylococcal community-acquired pneumonia group

| Variables                          | Total (n = 196) | Survivors (n = 165) | Non-survivors (n = 31) |
|-----------------------------------|----------------|---------------------|------------------------|
| Methicillin-resistant *Staphylococcus aureus* | 77 (39.3)   | 61 (37.0)           | 16 (51.6)             |
| All co-detection                  | 142 (72.4)    | 123 (74.5)          | 19 (61.3)             |
| Gram-positive pathogens           | 43 (21.9)     | 38 (23.0)           | 5 (16.1)              |
| *Streptococcus pneumoniae*        | 29 (14.8)     | 27 (16.4)           | 2 (6.5)               |
| Gram-negative pathogens           | 99 (50.5)     | 85 (51.5)           | 14 (45.2)             |
| *Klebsiella pneumoniae*           | 30 (15.3)     | 25 (15.2)           | 5 (16.1)              |
| *Pseudomonas aeruginosa*          | 16 (8.2)      | 12 (7.3)            | 4 (12.9)              |
| *Haemophilus influenzae*          | 12 (6.1)      | 12 (7.3)            | 0                     |
| Influenza virus                   | 1 (0.5)       | 1 (0.6)             | 1 (3.2)               |
| Bacteremia                        | 13 (6.6)      | 9 (5.4)             | 4 (12.9)              |

The appropriateness of antibiotics was assessed in 193 of the 196 patients; 77 (39%) received inappropriate initial antibiotics, and 116 (60%) received appropriate initial antibiotics. Anti-MRSA antibiotics were administered to only 6 patients (6/196); only 8% (6/77) of the patients with MRSA received appropriate antibiotics.
**Risk factors for 30-day mortality**

We performed a univariate analysis using the 26 baseline characteristics shown in Table 2. The results showed five variables with p-values ≤0.05. These variables were non-ambulatory status, GCS ≤ 12, albumin < 3.0 g/dL, pH < 7.35 and PaO2/FiO2 ≤ 250 (Table 4).

Table 4  Risk factors for 30-day mortality in the *S. aureus* community-acquired pneumonia group

| Variables                  | Univariate analysis |                      | Multivariate analysis |                      |
|----------------------------|---------------------|----------------------|-----------------------|----------------------|
|                            | Crude risks         | 95 % CI              | OR value              | 95 % CI              | P value              |
| Sex, male                  | 1.11 (0.50–2.43)    | 0.804                | 0.89 (0.36–2.16)     | 0.788                |
| Age ≥80 years              | 1.28 (0.59–2.76)    | 0.528                | 0.79 (0.33–1.92)     | 0.608                |
| Non-ambulatory status      | 3.58 (1.58–8.10)    | 0.001                | 2.40 (0.93–6.17)     | 0.070                |
| GCS ≤12                    | 2.84 (1.30–6.23)    | 0.007                | 1.40 (0.56–3.47)     | 0.469                |
| Albumin <3.0 g/dL          | 2.63 (1.18–5.85)    | 0.015                | 2.41 (1.01–5.83)     | 0.047                |
| pH <7.35                   | 2.58 (1.01–6.58)    | 0.046                | 2.19 (0.78–6.17)     | 0.140                |
| PaO2/FiO2 ≤250             | 4.27 (1.66–10.97)   | 0.001                | 3.29 (1.20–9.04)     | 0.021                |
| Methicillin resistance     | 1.82 (0.84–3.94)    | 0.126                | 1.17 (0.49–2.74)     | 0.727                |

OR: odds ratio
CI: confidence interval
GCS: Glasgow Coma Scale
PaO2/FiO2: ratio of arterial oxygen partial pressure to fractional inspired oxygen

To identify the mortality risk factors for patients with *S. aureus* CAP, we performed a multivariate analysis using the 5 significant variables in addition to age, sex, and presence of methicillin resistance. Table 4 shows the independent risk factors for 30-day mortality including PaO2/FiO2 ≤ 250 (adjusted odds ratio [AOR], 3.29; 95% confidence interval [CI] 1.20–9.04; p = 0.021) and albumin < 3.0 g/dL (AOR, 2.41; 95% CI 1.01–5.83; p = 0.047). Non-ambulatory status (AOR, 2.40; 95% CI 0.93–6.17; p = 0.070) tended to increase the mortality risk, although it was not statistically significant. The presence of methicillin resistance (AOR, 1.17; 95% CI 0.50–2.74; p = 0.727) was not detected as a significant risk factor.

**Subgroup analyses**

To compare the mortality risk factors between the *S. aureus* and pneumococcal CAP groups, we performed a further analysis to assess the risk factors for 30-day mortality in pneumococcal CAP (Supplemental Table 1). We identified 198 patients with pneumococcal CAP, with a 30-day mortality of 7.1% (14 of 198 patients). When performing the analysis of mortality risk factors for the pneumococcal CAP patients, we assessed the same 26 variables employed for the *S. aureus* CAP patients. The univariate analysis results showed that the variables (age ≥ 80 years, non-ambulatory status, GCS ≤ 12, albumin < 3.0 g/dL, neoplastic diseases, congestive heart failure, chronic renal diseases, glucose ≤ 60 or ≥ 300 mg/dL, blood urea nitrogen ≥ 30 mg/dL, and pleural effusion) had significant p-values (p ≤ 0.05). Using these variables, we performed a multivariate logistic analysis to compare mortality risk factors between the two pathogen groups. The following host factors were identified as associated with 30-day mortality in pneumococcal CAP: non-ambulatory status (AOR, 16.1; 95% CI 2.6–98.9; p = 0.003), albumin < 3.0 g/dL
Predictors of mortality in *S. aureus* CAP

Predictors of mortality in *S. aureus* CAP (AOR, 10.2; 95% CI 1.8–55.8, \( p = 0.007 \)) and age ≥ 80 years (AOR, 4.9; 95% CI 0.98–24.6; \( p = 0.052 \)).

**DISCUSSION**

In this post hoc analysis of a multicenter prospective observational study, we identified two potential risk factors (respiratory failure \([\text{PaO}_2/\text{FiO}_2 \leq 250] \) and hypoalbuminemia \([\text{albumin} < 3.0 \text{ g/dL}] \)) associated with 30-day mortality in patients with *S. aureus* CAP. A non-ambulatory status also tended to increase the mortality risk. This study also implied the differences in types of risk factors for 30-day mortality between the *S. aureus* and pneumococcal CAP groups. Hypoalbuminemia and non-ambulatory status had similar trends to increase the mortality risk in both groups. However, effects of advanced age and respiratory failure differed between the two groups.

As for clinical characteristics, the patients with *S. aureus* CAP in our study had distinct clinical features compared with the patients with pneumococcal CAP, which included advanced age, CNS disorders, poor functional ability, altered mental status, hypoalbuminemia, hyponatremia/hypernatremia, acidemia, hypoxemia, and bilateral lung involvement. These are well-known risk factors for mortality in all patients with CAP.9,17,18,21,22 Regarding the microbiological findings, we noted that the rate of co-infections in the *S. aureus* CAP group was surprisingly high (72%). The most detected co-infective organisms were Gram-negative pathogens, including *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*. Physicians should recognize these co-infections and consider using appropriate antibiotics for these co-infection pathogens.

To develop predictive rules, several prior studies have emphasized the potential mortality risk factors in CAP. The two most representative rules are the Pneumonia Severity Index8 and CURB-65.9 Assessing the severity at the pneumonia diagnosis is useful for determining the initial site of care. The current predictive scoring systems were developed using data from time points where information on the causative pathogens was not available in many cases. However, the patient care strategy might need modifications several days after the pneumonia diagnosis and once information on the causative pathogen has been obtained. Furthermore, the types and weight of risk factors for adverse outcomes might differ among patients with CAP according to the causative organisms. A previous study revealed that the microbial etiology of pneumonia was a mortality risk factor.10 Self et al compared the clinical outcomes of *S. aureus* CAP with those of pneumococcal CAP and reported more severe clinical outcomes for MRSA CAP than for pneumococcal CAP.23 In fact, this study showed a higher patient mortality proportion (16%) in *S. aureus* CAP than in pneumococcal CAP (7%), with MRSA mortality proportion of 20%, which suggests the importance of the pathogens identified in the patients. In this study, we focused on *S. aureus* because the prevalence of this organism is increasing as a causative pathogen in CAP.2,24,25

Our study revealed the mortality risk factors for patients with *S. aureus* CAP, which include respiratory failure and hypoalbuminemia. Previous studies have mainly focused on MRSA, with few studies focusing on both types of *S. aureus* CAP. Our study is therefore one of the few to assess the factors associated with outcomes in *S. aureus* CAP. The existing studies, which mainly focused on MRSA, have sought to identify the association between poor outcomes and microbial factors such as PVL and SCCmeC type.3,13,14,26 Although several studies have shown an association between these microbial factors and mortality,3,26 an important issue in these analyses was whether the host factors were assessed as confounders for mortality. In a previous retrospective study aimed at investigating the role of the microbial characteristics in predicting mortality in patients with MRSA, the results showed that these microbial characteristics (eg,
SCCmec type and PVL detection) were not significantly associated with 30-day mortality or with the duration of post-infection hospital stays after adjusting for other confounders. Another study that investigated the impact of PVL on the outcome of S. aureus pneumonia identified no significant associations between clinical outcomes and the presence of PVL or the in vitro level of alpha-hemolysin production. Our study also showed that a microbial factor, methicillin resistance, was not associated with mortality. Therefore, the microbial factors might not be the primary determinant for outcomes among patients with S. aureus CAP, and attention should be paid to important host factors as that could play a more significant role.

In our subanalysis, we assessed the differences in types of risk factors between the S. aureus and pneumococcal CAP groups. First, hypoalbuminemia and non-ambulatory status were common factors predicting mortality in both the S. aureus and pneumococcal CAP groups. These factors were previously reported as prognostic factors in CAP, although the PSI and CURB-65 do not include these factors. Second, in pneumococcal CAP, advanced age was associated with a high mortality risk, whereas PaO2/FiO2 ≤250 did not significantly affect mortality. In contrast, respiratory failure was a stronger risk factor than advanced age (age ≥80 years) in S. aureus CAP. This finding highlights the importance of respiratory failure in predicting the prognosis of S. aureus CAP, regardless of patient age. Furthermore, our findings suggest that factors associated with poor outcomes might differ according to the causative pathogens, and physicians should reconsider the risk factors for poor outcomes after obtaining information on the causative pathogen.

Our study will facilitate early clinical decision making for patients with S. aureus CAP, especially those at high mortality risk. When S. aureus is suspected as the causative organism of pneumonia from Gram staining, when patients have risk factors for S. aureus infection, or when S. aureus is microbiologically proven, physicians should expect that these patients with the mentioned risk factors will have a high mortality risk. Therefore, early multidimensional therapy such as appropriate respiratory management, improving nutritional status, the use of adjunctive therapy, and appropriate antibiotic treatment for these patients should be considered to improve their outcomes.

Our study had several limitations. First, we had a limited sample size, and the number of deaths at 30 days was insufficient to accurately estimate the prognostic risk factors. Second, although numerous studies have reported high rates of S. aureus and influenza virus co-infection, which are associated with poor outcomes, our study period could not include part of the influenza season because a greater than expected number of patients with pneumonia were registered. Third, the pathogens identified in this study might not have been the cause of the pneumonia. Fourth, our study did not assess microbial characteristics such as virulence and infectivity. Lastly, we could not sufficiently assess the association between mortality and the appropriateness of antimicrobial treatment. Further studies to assess the appropriateness of antibiotics are warranted.

In conclusion, patients with S. aureus CAP have distinct clinical features, and their most influential factors associated with mortality were respiratory failure and hypoalbuminemia. A number of potential host factors influencing mortality might be shared between S. aureus and pneumococcal CAP but might differ slightly. Physicians should recognize these findings and perform appropriate management strategies after obtaining information on the causative pathogen.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest on this project.

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Appendix: Supplementary data

Suppl Table 1 Univariate analysis for 30-day mortality in *Staphylococcus aureus* and pneumococcal community-acquired pneumonia

| Variables                        | *Staphylococcus aureus* | P value | *Pneumococcus* | P value |
|----------------------------------|-------------------------|---------|----------------|---------|
| Age ≥80 years                     | 1.28 (0.59–2.76)        | 0.528   | 9.56 (2.56–35.68) | <0.001 |
| Sex, male                        | 1.11 (0.50–2.43)        | 0.804   | 1.22 (0.41–3.67)  | 0.721   |
| Comorbidities                     |                         |         |                 |         |
| Neoplastic diseases              | 1.25 (0.43–3.60)        | 0.776   | 4.83 (1.47–15.89) | 0.016   |
| Chronic lung diseases            | 0.60 (0.24–1.48)        | 0.263   | 1.10 (0.33–3.68)  | 0.999   |
| Congestive heart failure         | 1.28 (0.48–3.43)        | 0.602   | 6.29 (1.70–23.31) | 0.014   |
| Chronic renal diseases           | 0.88 (0.18–4.14)        | 0.999   | 6.29 (1.70–23.31) | 0.014   |
| Chronic liver diseases           | 1.07 (0.12–9.46)        | 0.999   | 0.93 (0.89–0.96)  | 0.999   |
| Central nervous system disorders | 1.37 (0.62–3.04)        | 0.433   | 3.11 (0.89–10.79) | 0.082   |
| Diabetes                         | 0.76 (0.25–2.34)        | 0.791   | 1.30 (0.34–4.91)  | 0.717   |
| Immunosuppression                | 1.50 (0.40–5.72)        | 0.468   | 0.92 (0.88–0.96)  | 0.373   |
| Non-ambulatory status            | 3.58 (1.58–8.10)        | 0.001   | 24.44 (6.36–93.99) | <0.001 |
| Physical findings                |                         |         |                 |         |
| Glasgow Coma Scale ≤12           | 2.84 (1.30–6.23)        | 0.007   | 5.83 (1.74–19.51) | 0.009   |
| Pulse rate ≥125 beats per min    | 1.48 (0.51–4.31)        | 0.549   | 2.68 (0.68–10.55) | 0.155   |
| Systolic blood pressure <90 mm Hg| 1.67 (0.57–4.93)        | 0.355   | 1.01 (0.12–8.35)  | 0.999   |
| Respiration rate ≥30 breaths per min| 2.16 (0.96–4.86)    | 0.072   | 2.11 (0.67–6.65)  | 0.194   |
| Laboratory findings              |                         |         |                 |         |
| Hematocrit <0.3                  | 0.94 (0.33–2.66)        | 0.999   | 3.28 (0.94–11.44) | 0.072   |
| Platelet count <120,000/mm³      | 1.60 (0.49–5.22)        | 0.495   | 1.01 (0.12–8.35)  | 0.999   |
| Albumin <3.0 g/dL                | 2.63 (1.18–5.85)        | 0.015   | 18.40 (3.97–85.34) | <0.001 |
| Glucose ≤60 or ≥300 mg/dL        | 2.30 (0.67–7.85)        | 0.244   | 6.00 (1.39–25.84) | 0.033   |
| Blood urea nitrogen ≥30 mg/dL    | 2.05 (0.93–4.53)        | 0.073   | 5.48 (1.79–16.79) | 0.003   |
| Na <130 or ≥150 mEq/L            | 2.00 (0.77–5.22)        | 0.164   | 4.29 (1.04–17.69) | 0.064   |
| Creatinine ≥1.2                  | 1.08 (0.41–2.86)        | 0.806   | 2.14 (0.68–6.74)  | 0.190   |
| pH <7.35                         | 2.58 (1.01–6.58)        | 0.046   | 0.98 (0.12–8.11)  | 0.999   |
| PaO₂/FiO₂ ≤250                   | 4.27 (1.66–10.97)       | 0.001   | 3.006 (1.0–9.08)  | 0.071   |
| Radiographic findings            |                         |         |                 |         |
| Bilateral lung involvement       | 1.52 (0.68–3.36)        | 0.305   | 2.62 (0.84–8.12)  | 0.086   |
| Pleural effusion                 | 1.35 (0.59–3.10)        | 0.476   | 10.03 (3.13–32.15) | 0.001  |

OR: odds ratio
CI: confidence interval
PaO₂/FiO₂: ratio of arterial oxygen partial pressure to fractional inspired oxygen

Data are present as number and percentage.

Immunosuppression included any immunosuppressive diseases such as congenital and acquired immunodeficiency, hematological diseases, and neutropenia (<1000/mm³); treatment with immunosuppressive drugs within the previous 30 days; and corticosteroids dosages of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.

Non-ambulatory status was defined as being bedridden or using a wheelchair because of difficulty walking.