Clinical Characteristics of Influenza-Associated Pneumonia of Adults: Clinical Features and Factors Contributing to Severity and Mortality

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Background: Pneumonia is a major complication of influenza that contributes to mortality. Clinical characteristics and factors of influenza virus contributing to the severity and mortality of pneumonia have not been fully elucidated. Objective: The objective was to clarify clinical characteristics and factors contributing to the severity and mortality of influenza-associated pneumonia (flu-p†).

Methods: We retrospectively analyzed patients with flu-p. Results: From December 1999 to March 2016, 210 patients with a median age of 69 (range, 17 to 92) years with flu-p based on positive rapid antigen tests, increased antibody titers of paired sera, or positive results of reverse transcription polymerase chain reaction were admitted to our institution. A multivariate analysis found that advanced age (≥ 65 years), pneumonia subtypes (unclassified), diabetes mellitus, and acute kidney injury complicated with flu-p were independent factors associated with disease severity, whereas pneumonia subtypes (mixed viral and bacterial pneumonia and unclassified), healthcare-associated pneumonia, acute kidney injury complicated with flu-p, and severity on admission (severe) were independent factors associated with non-survival.

Conclusion: The clinical characteristics of flu-p are varied, and the contribution of several factors to the severity and mortality of flu-p suggest their importance in either preventing flu-p or managing flu-p after it develops.

INTRODUCTION

The influenza pandemic in 2009 had a strong effect on clinical practice, and pneumonia is the leading complication of influenza virus infection [1]. Globally, influenza causes significant morbidity and mortality that respectively result in severe illness in 3 to 5 million people and death in up to 500,000 during epidemic years [2]. Of the complications of influenza, pneumonia is the most serious. The excess morbidity and mortality associated with influenza epidemics are generally reflected by high rates of pneumonia and hospitalization associated with...
Table 1. Patient Characteristics.

| Characteristic                  | Total     | Primary viral pneumonia | Mixed viral and bacterial pneumonia | Secondary pneumonia | Unclassified | P-value  |
|--------------------------------|-----------|-------------------------|-------------------------------------|---------------------|--------------|----------|
| Age (years)                    | 66.7 ± 15.63 | 66.7 ± 15.91           | 67.4 ± 14.44                       | 61.7 ± 16.91       | 71.0 ± 15.34 | 0.118    |
| Male sex                       | 151 (71.9%) | 59 (77.6%)             | 55 (77.5%)                         | 22 (64.7%)         | 15 (51.7%)   | 0.029    |
| Smoking history                | 134 (63.8%) | 52 (68.4%)             | 46 (64.8%)                         | 22 (64.7%)         | 14 (48.3%)   | 0.287    |
| Vaccination history            |           |                        |                                     |                     |              |          |
| 23-valent polysaccharide vaccine (within 5 years) | | | | | | |
| Yes                            | 7 (3.3%)   | 3 (3.9%)                | 2 (2.8%)                           | 1 (2.9%)            | 1 (3.4%)     | 0.555    |
| No                             | 201 (95.7%)| 73 (96.1%)              | 69 (97.2%)                         | 32 (94.1%)         | 27 (93.1%)   |          |
| Unknown                        | 2 (1.0%)   | 0 (0.0%)                | 0 (0.0%)                           | 1 (2.9%)            | 1 (3.4%)     |          |
| Influenza vaccine (within one year) | | | | | | |
| Yes                            | 31 (14.8%) | 10 (13.2%)              | 10 (14.1%)                         | 7 (20.6%)           | 4 (13.8%)    | 0.012    |
| No                             | 129 (61.4%)| 57 (75.0%)              | 44 (62.0%)                         | 15 (44.1%)         | 13 (44.8%)   |          |
| Unknown                        | 50 (23.8%) | 9 (11.8%)               | 17 (23.9%)                         | 12 (35.3%)         | 12 (41.4%)   |          |
| CAP/HCAP                        | 64 (30.5%) | 25 (32.9%)              | 23 (32.4%)                         | 6 (17.6%)           | 10 (34.5%)   | 0.363    |
| Viral subtypes                 |           |                        |                                     |                     |              |          |
| pH1N1                          | 48 (22.9%) | 19 (25.0%)              | 21 (29.6%)                         | 6 (17.8%)           | 2 (6.9%)     | 0.004    |
| H3N2                           | 8 (3.8%)   | 1 (1.3%)                | 2 (2.8%)                           | 3 (8.8%)            | 2 (6.9%)     |          |
| sH1N1                          | 23 (11.0%) | 16 (21.1%)              | 5 (7.0%)                           | 2 (5.9%)            | 0 (0.0%)     |          |
| Undifferentiated               | 85 (40.5%) | 27 (35.5%)              | 25 (35.2%)                         | 18 (52.9%)          | 15 (51.7%)   |          |
| B                              | 46 (21.9%) | 13 (17.1%)              | 18 (25.4%)                         | 5 (14.7%)           | 10 (34.5%)   |          |
| Comorbidity                    |           |                        |                                     |                     |              |          |
| Chronic pulmonary disease      | 95 (45.2%) | 31 (40.8%)              | 34 (47.9%)                         | 14 (41.2%)          | 16 (55.2%)   | 0.534    |
| Chronic obstructive pulmonary disease | 41 (19.5%) | 11 (14.5%)              | 22 (31.0%)                         | 4 (11.8%)           | 4 (13.8%)    | 0.028    |
| Asthma                         | 20 (9.5%)  | 11 (14.5%)              | 2 (2.8%)                           | 4 (11.8%)           | 3 (10.3%)    | 0.107    |
| Bronchiectasis                 | 10 (4.8%)  | 0 (0.0%)                | 8 (11.3%)                          | 0 (0.0%)            | 2 (6.9%)     | 0.006    |
| Nontuberculous mycobacteriosis | 4 (1.9%)   | 0 (0.0%)                | 3 (4.2%)                           | 0 (0.0%)            | 1 (3.4%)     | 0.208    |
| Old pulmonary tuberculosis     | 14 (6.7%)  | 5 (6.6%)                | 1 (1.4%)                           | 5 (14.7%)           | 3 (10.3%)    | 0.062    |
| Chronic pulmonary aspergilosis | 2 (1.0%)   | 0 (0.0%)                | 0 (0.0%)                           | 1 (2.9%)            | 1 (3.4%)     | 0.191    |
| Interstitial pneumonia         | 15 (7.1%)  | 6 (7.9%)                | 4 (5.6%)                           | 2 (5.9%)            | 3 (10.3%)    | 0.840    |
| Post lung cancer operation     | 4 (1.9%)   | 3 (3.9%)                | 0 (0.0%)                           | 0 (0.0%)            | 1 (3.4%)     | 0.250    |
| Hypertension                   | 26 (12.4%) | 7 (9.2%)                | 10 (14.1%)                         | 4 (11.8%)           | 5 (17.2%)    | 0.674    |
| Chronic cardiac disease        | 30 (14.3%) | 15 (19.7%)              | 6 (8.5%)                           | 5 (14.7%)           | 4 (13.8%)    | 0.281    |
| Congestive heart failure       | 12 (5.7%)  | 5 (6.6%)                | 3 (4.2%)                           | 1 (2.9%)            | 3 (10.3%)    | 0.565    |
| Ischemic heart disease         | 14 (6.7%)  | 7 (9.2%)                | 4 (5.6%)                           | 3 (8.8%)            | 0 (0.0%)     | 0.356    |
| Valvular heart disease         | 5 (2.4%)   | 4 (5.3%)                | 0 (0.0%)                           | 1 (2.9%)            | 0 (0.0%)     | 0.158    |
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Influenza. Influenza-associated pneumonia (flu-p) is an independent factor of mortality [3]; however, there are few reports on the clinical features, treatment, and factors contributing to the severity and mortality of flu-p [4]. Increased understanding of these factors is expected to lead to appropriate prevention and management of flu-p and mitigate negative outcomes. Therefore, the purpose of this study was to investigate the clinical features and factors contributing to the severity and mortality of flu-p.

### Table 1, cont’d. Patient Characteristics.

| Complications | 0  | 1-2 | 3-4 | Unknown | Severe | Mortality |
|---------------|----|-----|-----|---------|--------|-----------|
| Pneumothorax  | 4 (1.9%) | 0 (0.0%) | 1 (1.4%) | 0 (0.0%) | 3 (10.3%) | 0.004 |
| Pleuritis or pyothorax | 2 (1.0%) | 0 (0.0%) | 2 (2.8%) | 0 (0.0%) | 0 (0.0%) | 0.267 |
| Acute kidney disease | 7 (3.3%) | 2 (2.6%) | 5 (7.0%) | 0 (0.0%) | 0 (0.0%) | 0.150 |
| Acute pulmonary thromboembolism | 2 (1.0%) | 2 (2.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.313 |
| Myocarditis | 2 (1.0%) | 1 (1.3%) | 0 (0.0%) | 1 (2.9%) | 0 (0.0%) | 0.476 |
| Neurological symptoms (encephalitis, meningitis) | 7 (3.3%) | 5 (6.6%) | 2 (2.8%) | 0 (0.0%) | 0 (0.0%) | 0.194 |
| Rhabdomyolysis | 13 (6.2%) | 6 (7.9%) | 7 (9.9%) | 0 (0.0%) | 0 (0.0%) | 0.103 |
| Performance status | | | | | | |
| 0 | 102 (48.6%) | 41 (53.9%) | 31 (43.7%) | 23 (67.6%) | 7 (24.1%) | 0.027 |
| 1-2 | 42 (20.0%) | 11 (14.5%) | 18 (25.4%) | 6 (17.6%) | 7 (24.1%) | |
| 3-4 | 20 (9.5%) | 5 (6.6%) | 8 (11.3%) | 3 (8.8%) | 4 (13.8%) | |
| Unknown | 46 (21.9%) | 19 (25.0%) | 14 (19.7%) | 2 (5.9%) | 11 (37.9%) | |
| Severe | 56 (26.7%) | 17 (22.4%) | 20 (28.2%) | 6 (17.6%) | 13 (44.8%) | 0.069 |
| Mortality | 16 (7.6%) | 1 (1.3%) | 8 (11.3%) | 2 (5.9%) | 5 (17.2%) | 0.022 |

AST, aspartate transaminase; BUN, blood urea nitrogen; CAP, community-acquired pneumonia; Cre, creatinine; CRP, C-reactive protein; HCAP, healthcare-associated pneumonia; LDH, lactate dehydrogenase; WBC, white blood cells.
PATIENTS AND METHODS

We conducted a retrospective study of consecutive patients hospitalized with flu-p from December 1999 through March 2016 at our institution in Saitama, Japan. The performance status (PS) [5] of the patients’ in performing daily life activities before the development of pneumonia was recorded on admission based on anamnesis from the patients and their families. Excluded patients comprised those showing immunosuppression (AIDS or receiving chemotherapy) and those with tuberculosis, non-resected lung cancer, or confirmed alternative diagnosis lasting until the end of the follow-up period.

Healthcare-associated pneumonia (HCAP) was defined according to the criteria of the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines [6]. Diagnosis of causative microorganisms was based on results of semi-quantitative culture of respiratory samples or blood, paired sera, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, and reverse transcription polymerase chain reaction (RT-PCR), as reported previously [7,8]. The types of flu-p were judged by respiratory physicians based on a previous report [9]. Patients with flu-p with an incomplete work-up of mixed infection or anamnesis were classified as having an “unclassified” pneumonia subtype. Severe pneumonia was defined when at least one major criterion or three minor criteria of the IDSA/ATS guidelines [10] were present. Complications were counted as described in a previous report [11]. The definition of acute kidney injury can be found elsewhere [12]. Approval for this study was obtained from the institutional clinical research ethics board of Saitama Cardiovascular and Respiratory Center (no. 2016003).

Statistical Analysis

Data are presented using descriptive statistics for continuous variables and frequencies for categorical variables. Differences between groups were analyzed with analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Risk factors for severe pneumonia and mortality were evaluated by univariate and multivariate logistic regression analyses. Variables that were considered to be relevant or found to be significant by the univariate analysis were included in the multivariate logistic regression analysis. With respect to the events of mortality, Firth’s bias correction was used to alleviate the small number of the events in the logistic analyses [13]. A two-sided *P* value < 0.05 was considered statistically significant in all tests. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Patients

From December 1999 to March 2016, 210 patients ≥ 18 years old with flu-p were admitted to our institution. The median patient age was 69 (range, 17 to 92) years, and 151 (71.9 percent) were men (Table 1). One hundred thirty-three patients had a smoking history, and 12 had

| Method                        | No. of episodes studied | No. of positive diagnostic studies (%) |
|-------------------------------|-------------------------|----------------------------------------|
| Paired sera                   | 157                     | 13 (82)                                |
| Rapid influenza diagnostic test| 208                     | -                                      |
| RT-PCR                        | 12                      | -                                      |
| Urinary antigen               |                         |                                        |
| *Streptococcus pneumoniae*    | 178                     | 48 (24)                                |
| *Legionella sp.*              | 178                     | 2 (1)                                  |
| Culture                       |                         |                                        |
| Sputum                        | 176                     | 41 (23)                                |
| Transbronchial aspirate       | 10                      | 2 (20)                                 |
| Protected specimen brush      | 2                       | 0 (0)                                  |
| Bronchial washing             | 3                       | 0 (0)                                  |
| Bronchoalveolar lavage fluid  | 16                      | 2 (13)                                 |
| Blood                         | 140                     | 3 (2)                                  |
| Pleural fluid                 | 3                       | 0 (0)                                  |

RT-PCR, reverse-transcription polymerase chain reaction.
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Table 3. Mixed infection with influenza virus.

| Pathogens | Total | % of 210 patients | Severe | Non-survivors |
|-----------|-------|------------------|--------|--------------|
|           | n     |                  | n      | n            |
| Two pathogens |       |                  |        |              |
| *Streptococcus pneumoniae* + *Chlamydia pneumoniae* | 3 | 1.4 | 2 | 0 |
| *S. pneumoniae* + *Mycoplasma pneumoniae* | 2 | 1.0 | 0 | 0 |
| *S. pneumoniae* + *MSSA* | 2 | 1.0 | 2 | 1 |
| *S. pneumoniae* + *Haemophilus influenzae* | 1 | 0.5 | 0 | 0 |
| *S. pneumoniae* + *Legionella spp.* | 1 | 0.5 | 0 | 0 |
| *S. pneumoniae* + *Staphylococcus haemolyticus* | 1 | 0.5 | 1 | 1 |
| *S. pneumoniae* + *Aspergillus fumigatus* | 1 | 0.5 | 0 | 0 |
| *P. aeruginosa* + *Acinetobacter baumannii* | 1 | 0.5 | 0 | 0 |
| Single pathogen |       |                  |        |              |
| *S. pneumoniae* | 44 | 21.0 | 9 | 1 |
| *H. influenza* | 9 | 4.3 | 3 | 1 |
| *M. pneumoniae* | 6 | 2.9 | 1 | 1 |
| GNEB | 4 | 1.9 | 2 | 1 |
| *C. pneumoniae* | 4 | 1.9 | 1 | 1 |
| *Legionella sp.* | 3 | 1.4 | 0 | 0 |
| *P. aeruginosa* | 2 | 1.0 | 1 | 0 |
| MRSA | 2 | 1.0 | 1 | 1 |
| MSSA | 1 | 0.5 | 0 | 0 |
| *Moraxella catarrhalis* | 1 | 0.5 | 0 | 0 |
| *S. pyogenes* | 1 | 0.5 | 0 | 0 |
| A. fumigatus | 2 | 1.0 | 1 | 1 |

GNEB, gram-negative enterobacilli; MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus.

received long-term oxygen therapy. Charlson’s comorbidity index was low in 87, medium in 115, high in 7, and very high in 1 patient. Body mass index was ≥ 25 kg/m² in 22 patients and < 18 kg/m² in 33. Patients’ PS as classified by the Eastern Cooperative Oncology Group [5] included PS 0 in 102, PS 1-2 in 42, PS 3-4 in 40, and unknown in 46 patients. Only 7 patients received 23-valent pneumococcal vaccine, and 31 patients received influenza vaccine. Of the 24 patients who were treated with neuraminidase inhibitors (NI) before presenting to our hospital, half had received NI within 48 hours after onset of initial symptoms. The pneumonia subtypes included primary viral pneumonia (n = 76, 36.2 percent), mixed viral and bacterial pneumonia (n = 71, 33.8 percent), secondary bacterial pneumonia (n = 34, 16.2 percent), and unclassified pneumonia (n = 29, 13.8 percent). The reason for the pneumonia subtype being “unclassified” was an incomplete work-up of mixed infection in 6 patients and incomplete anamnesis in 23 patients. None of the female patients were pregnant. Among the four flu-p subtypes, the ratio of men, vaccination history of influenza vaccine within one year, and incidences of chronic obstructive pulmonary disease (COPD), bronchiectasis, and premorbid PS differed significantly (Table 1).

**Viral Subtypes**

Diagnosis of viral subtypes was based on an influenza rapid diagnostic test in 154 patients, increased antibody titers in 82 patients, and positive RT-PCR in 12 patients (Table 2). The viral subtypes included pH1N1 (n = 23, 11.0 percent), H3N2 (n = 48, 22.9 percent), seasonal H1N1 (sH1N1) (n = 8, 3.8 percent), B (n = 46, 21.9 percent), and A but with subtypes not differentiated (n = 85, 40.5 percent).

**Etiology of Mixed Infection**
Table 4. Univariate and multivariate analyses of factors contributing to severe pneumonia.

|                          | N     | Severe (%) | Univariate analysis | Multivariate analysis |
|--------------------------|-------|------------|---------------------|-----------------------|
|                          |       |            | Odds ratio (95% CI) | P-value               | Odds ratio (95% CI) | P-value               |
| **Sex**                  |       |            |                     |                       |                       |                       |
| Male                     | 151   | 38 (25.2%) | 0.77 (0.39, 1.49)   | 0.432                 |                       |                       |
| **Age**                  |       |            |                     |                       |                       |                       |
| 65-                      | 130   | 42 (32.3%) | 2.25 (1.14, 4.46)   | 0.020                 | 2.74 (1.07, 7.01)    | 0.036                 |
| <65                      | 80    | 14 (17.5%) |                       |                       |                       |                       |
| **Body mass index**      |       |            |                     |                       |                       |                       |
| BMI unknown              | 78    | 27 (34.6%) | 2.19 (1.05, 4.55)   | 0.036                 | 1.48 (0.60, 3.65)    | 0.391                 |
| BMI≥25                   | 22    | 5 (22.7%)  | 1.22 (0.39, 3.82)   | 0.738                 | 1.31 (0.34, 5.01)    | 0.697                 |
| 18>BMI                   | 33    | 9 (27.3%)  | 1.55 (0.60, 4.01)   | 0.367                 | 1.13 (0.35, 3.62)    | 0.839                 |
| 25>BMI≥18                | 77    | 15 (19.5%) | Reference           |                       | Reference             |                       |
| **Vaccination history**  |       |            |                     |                       |                       |                       |
| 23-valent pneumococcal   | Unknown| 2    | 0 (0.0%)            |                       |                       |                       |
| polysaccharide vaccination within 5 years | No    | 201  | 54 (26.9%) | 0.92 (0.17, 4.87) | 0.920               |                       |
|                          | Yes   | 7    | 2 (28.6%)          |                       |                       |                       |
| **Influenza vaccination**| Unknown| 50  | 11 (22.0%) | 0.81 (0.28, 2.31) | 0.695               |                       |
| within one year          | No    | 129  | 37 (28.7%) | 1.16 (0.47, 2.82) | 0.749               |                       |
|                          | Yes   | 31   | 8 (25.8%)          |                       |                       |                       |
| **Prior antibiotic treatment** | No    | 142  | 43 (30.3%) | 1.84 (0.91, 3.71) | 0.090               | 1.40 (0.61, 3.20)    | 0.423                 |
| **Neuraminidase inhibitors by local physicians** | No    | 186  | 52 (28.0%) | 1.94 (0.41, 9.16) | 0.402               |                       |
|                          | ≥48 h | 12   | 2 (16.7%)          | 1.00 (0.12, 8.56)    | 1.000               |                       |
|                          | <48 h | 12   | 2 (16.7%)          |                       | Reference           |                       |
| **Pneumonia subtype**    |       |            |                     |                       |                       |                       |
| Mixed viral and bacterial | 71    | 20 (28.2%) | 1.36 (0.64, 2.87) | 0.419                 | 1.24 (0.39, 3.97)    | 0.717                 |
| Secondary bacterial      | 34    | 6 (17.6%)  | 0.74 (0.26, 2.09)   | 0.574                 | 1.56 (0.42, 5.86)    | 0.508                 |
| Unclassified             | 29    | 13 (44.8%) | 2.82 (1.14, 7.00)   | 0.025                 | 3.31 (1.07, 10.28)   | 0.038                 |
| **Viral subtype**        |       |            |                     |                       |                       |                       |
| A/H1N1 seasonal          | 8     | 1 (12.5%)  | 0.48 (0.05, 4.34)   | 0.514                 | 0.71 (0.07, 7.23)    | 0.770                 |
| pH1N1                    | 23    | 5 (21.7%)  | 0.93 (0.28, 3.10)   | 0.912                 | 2.88 (0.64, 12.96)   | 0.168                 |
| A/Undifferentiated       | 85    | 28 (32.9%) | 1.65 (0.73, 3.72)   | 0.225                 | 1.95 (0.71, 5.38)    | 0.196                 |
| B                        | 46    | 11 (23.9%) | 1.06 (0.41, 2.75)   | 0.909                 | 1.05 (0.34, 3.30)    | 0.928                 |
| A/H3N2                   | 48    | 11 (22.9%) | Reference           |                       | Reference             |                       |
| Mixed infection          | Yes   | 87   | 22 (25.3%) | 0.89 (0.47, 1.65)   | 0.704               | 1.20 (0.44, 3.28)    | 0.729                 |
### Table 4, cont’d. Univariate and multivariate analyses of factors contributing to severe pneumonia.

| Comorbidity                        | Yes | No (%) | Odds Ratio (95% CI) | p-value | Odds Ratio (95% CI) | p-value |
|-----------------------------------|-----|--------|---------------------|---------|---------------------|---------|
| Chronic pulmonary diseases        | Yes | 95     | 25 (26.3%)          | 0.97 (0.52, 1.79) | 0.917 (0.44, 1.94) | 0.828 |
| COPD                              | Yes | 41     | 10 (24.4%)          | 0.86 (0.39, 1.90) | 0.713               |         |
| Asthma                            | Yes | 20     | 3 (15.0%)           | 0.46 (0.13, 1.62) | 0.225               |         |
| Bronchiectasis                    | Yes | 10     | 3 (30.0%)           | 1.19 (0.30, 4.77) | 0.807               |         |
| Pulmonary NTM                     | Yes | 4      | 0 (0.0%)            |         |                     |         |
| Interstitial pneumonia            | Yes | 15     | 6 (40.0%)           | 1.93 (0.66, 5.71) | 0.232               |         |
| Hypertension                      | Yes | 26     | 9 (34.6%)           | 1.54 (0.64, 3.70) | 0.330               |         |
| Chronic cardiac diseases          | Yes | 30     | 7 (23.3%)           | 0.81 (0.33, 2.02) | 0.656               |         |
| Congestive heart failure          | Yes | 12     | 4 (33.3%)           | 1.40 (0.41, 4.86) | 0.592               |         |
| Ischemic heart diseases           | Yes | 14     | 2 (14.3%)           | 0.44 (0.09, 2.02) | 0.290               |         |
| Diabetes mellitus                 | Yes | 27     | 11 (40.7%)          | 2.11 (0.91, 4.87) | 0.081 (2.74, 1.01) | 0.048 |
| Post surgery of upper digestive system | Yes | 4  | 2 (50.0%)          | 2.81 (0.39, 20.46) | 0.307               |         |
| Chronic liver diseases            | Yes | 7      | 1 (14.3%)           | 0.45 (0.05, 3.81) | 0.463               |         |
| Connective tissue diseases        | Yes | 9      | 1 (11.1%)           | 0.33 (0.04, 2.71) | 0.304               |         |
| Immunosuppression due to systemic corticosteroids or immunosuppressants | Yes | 20     | 4 (20.0%)           | 0.66 (0.21, 2.08) | 0.481               |         |
| Malignancy                        | Yes | 0      | 0 (0.0%)            |         |                     |         |
| Alcoholism                        | Yes | 2      | 0 (0.0%)            |         |                     |         |
| CKD                               | Yes | 0      | 0 (0.0%)            |         |                     |         |
| Neurological disorders            | Yes | 17     | 9 (52.9%)           | 3.49 (1.28, 9.57) | 0.015 (2.38, 0.67) | 0.180 |
| Smoking history                   | Yes | 134    | 31 (23.1%)          | 0.61 (0.33, 1.15) | 0.126               |         |
| Long-term oxygen therapy          | Yes | 12     | 3 (25.0%)           | 0.91 (0.24, 3.50) | 0.893               |         |
| HCAP/CAP                          | HCAP | 64     | 19 (29.7%)          | 1.24 (0.65, 2.39) | 0.513               |         |
| Performance status                | Unknown | 46 | 21 (45.7%) | 3.92 (1.81, 8.48) | <0.001 (2.32, 0.86) | 0.095 |
| PS 3-4                            | Yes | 20     | 6 (30.0%)           | 2.00 (0.68, 5.91) | 0.210 (0.68, 2.85) | 0.600 |
| PS 1-2                            | Yes | 42     | 11 (26.2%)          | 1.66 (0.70, 3.90) | 0.248 (1.20, 3.35) | 0.734 |
| PS 0                              | Yes | 102    | 18 (17.6%)          | Reference | Reference           |         |
| Charlson Comorbidity Index        | High, Very high | 8  | 3 (37.5%)           | 2.01 (0.44, 9.16) | 0.367               |         |
Severity on Admission

Overall, 56 patients (26.7 percent) had severe pneumonia. Severity tended to differ between the four groups ($P = 0.069$). Among the four pneumonia subtypes, the unclassified subtype included 13 patients with severe flu-p and comprised the highest number of severe cases.

Treatment and Outcomes

Twenty-four patients received NI before admission, half of whom received NI within 48 hours after the onset of initial symptoms, and 91 patients received NI after admission. Overall, 115 (54.8 percent) patients received antiviral therapy either before or after admission, with 53 (46.1 percent) receiving NI within 48 hours of their initial symptoms. Antibiotics were administered to 68 patients before admission by local physicians and to 202 patients following admission, with 128 receiving guideline-concordant therapy [10]. Among the 210 patients with flu-p, discordant therapy included single β-lactams in 77 patients and a single macrolide in 1 patient. Among the 105 patients with mixed viral and bacterial or secondary bacterial pneumonia, discordant therapy included single β-lactams in 37 patients and a single macrolide in 1 patient. Corticosteroid therapy was administered in 24 (11.4 percent) patients, and 17 (8.1 percent) patients required mechanical ventilation. On admission, 56 (26.7 percent) patients were judged to have severe pneumonia, and 16 (7.6 percent) patients died. Mortality differed significantly among the four pneumonia subtypes ($P = 0.022$), with the unclassified pneumonia subtype showing the highest

Complications of flu-p on Admission

The patients had several complications on admission: pneumothorax ($n = 4$, 1.9 percent), pyothorax ($n = 2$, 1.0 percent), acute kidney injury ($n = 7$, 3.3 percent), acute pulmonary thromboembolism ($n = 2$, 1.0 percent), cardiomyositis ($n = 2$, 1.0 percent), neurological complication ($n = 7$, 3.3 percent), and rhabdomyolysis ($n = 13$, 6.2 percent). The frequency of pneumothorax differed significantly among the four pneumonia subtypes ($P = 0.004$) (Table 1).

Laboratory Data on Admission

Laboratory data on admission (median, range) included a white blood cell count of 9,865/mm$^3$ (1300-37,200), AST of 31 IU/L (9-2,380), ALT of 22 IU/L (5-1,135), LDH of 260 IU/L (26-4,695), BUN of 17 mg/dL (5-145), creatinine of 0.8 mg/dL (0.3-3.4), and CRP of 12.1 mg/dL (0.2-54.3). The values of serum BUN ($P = 0.015$), creatinine ($P = 0.030$), and CRP ($P < 0.001$) differed significantly among the four pneumonia subtypes (Table 1).
Table 5. Univariate and multivariate analyses of factors contributing to mortality.

|                      | N   | Mortality (%) | Univariate analysis | Multivariate analysis |
|----------------------|-----|---------------|---------------------|-----------------------|
|                      |     |              | Odds ratio (95% CI) | P-value               |
|                      |     |              | Odds ratio (95% CI) | P-value               |
| Sex                  |     |              |                     |                       |
| Male                 | 151 | 12 (7.9%)    | 1.11 (0.36, 3.42)   | 0.862                 |
| Age                  |     |              |                     |                       |
| 65-                  | 130 | 11 (8.5%)    | 1.32 (0.46, 3.82)   | 0.607                 |
| Body mass index      |     |              |                     |                       |
| Unknown              | 78  | 10 (12.8%)   | 4.63 (1.11, 19.27)  | 0.035                 |
| ≥25                  | 22  | 2 (9.1%)     | 3.68 (0.58, 23.34)  | 0.167                 |
| 18>                  | 33  | 2 (6.1%)     | 2.40 (0.39, 14.80)  | 0.347                 |
| 25>BMI≥18            |     |              |                     |                       |
| Unknown              | 77  | 2 (2.6%)     | Reference           |                       |
| 23-valent pneumococcal polysaccharide vaccination within 5 years | | | | |
| No                   | 201 | 16 (8.0%)    | 1.33 (0.06, 29.67)  | 0.855                 |
| Influenza vaccination within one year | | | | |
| Unknown              | 50  | 2 (4.0%)     | 1.05 (0.13, 8.58)   | 0.965                 |
| No                   | 129 | 13 (10.1%)   | 2.36 (0.41, 13.68)  | 0.340                 |
| Prior antibiotic treatment | | | | |
| No                   | 142 | 8 (5.6%)     | 0.45 (0.16, 1.23)   | 0.119                 |
| Pneumonia subtype    |     |              |                     |                       |
| Mixed viral and bacterial | 71 | 8 (11.3%)    | 6.74 (1.14, 39.93)  | 0.036                 |
| Secondary bacterial  | 34  | 2 (5.9%)     | 3.87 (0.48, 31.17)  | 0.203                 |
| Unclassified         | 29  | 5 (17.2%)    | 11.30 (1.73, 73.99) | 0.011                 |
| Primary viral        | 76  | 1 (1.3%)     | Reference           | Reference             |
| Viral subtype        |     |              |                     |                       |
| A/H1N1 seasonal      | 8   | 0 (0.0%)     | 1.86 (0.06, 58.20)  | 0.723                 |
| pH1N1                | 23  | 1 (4.3%)     | 2.11 (0.20, 22.25)  | 0.534                 |
| A/Undifferentiated   | 85  | 11 (12.9%)   | 4.89 (0.84, 28.32)  | 0.077                 |
| B                    | 46  | 3 (6.5%)     | 2.55 (0.35, 18.39)  | 0.354                 |
| A/H3N2               | 48  | 1 (2.1%)     | Reference           | Reference             |
| Mixed infection      |     |              |                     |                       |
| Yes                  | 87  | 9 (10.3%)    | 1.88 (0.69, 5.13)   | 0.218                 |
| Comorbidities        |     |              |                     |                       |
| Chronic pulmonary diseases | Yes | 95 | 8 (8.4%) | 1.23 (0.45, 3.33) | 0.686 | 1.94 (0.60, 6.25) | 0.265 |
| COPD                 | Yes | 41 | 2 (4.9%) | 0.68 (0.17, 2.76) | 0.588 |
| Asthma               | Yes | 20 | 0 (0.0%) | 0.26 (0.01, 4.78) | 0.363 |
| Bronchiectasis       | Yes | 10 | 1 (10.0%) | 1.89 (0.29, 12.38) | 0.507 |
| Factor                                      | Yes | No (%) | Odds Ratio | 95% CI     | p-Value |
|---------------------------------------------|-----|--------|------------|------------|---------|
| **Pulmonary NTM**                           | Yes | 4      | 0 (0.0%)   | 1.28 (0.05, 34.96) | 0.882   |
| **Old tuberculosis**                        | Yes | 14     | 3 (21.4%)  | 4.14 (1.07, 16.07) | 0.040   |
| **Interstitial pneumonia**                  | Yes | 15     | 2 (13.3%)  | 2.32 (0.52, 10.32) | 0.270   |
| **Hypertension**                            | Yes | 26     | 2 (7.7%)   | 1.20 (0.29, 5.02)  | 0.803   |
| **Chronic cardiac diseases**                | Yes | 30     | 3 (10.0%)  | 1.58 (0.45, 5.57)  | 0.478   |
| **Congestive heart failure**                | Yes | 12     | 2 (16.7%)  | 3.03 (0.65, 14.03) | 0.156   |
| **Ischemic heart diseases**                 | Yes | 14     | 1 (7.1%)   | 1.30 (0.21, 8.05)  | 0.777   |
| **Arrhythmias**                             | Yes | 6      | 1 (16.7%)  | 3.33 (0.44, 25.08) | 0.242   |
| **Diabetes mellitus**                       | Yes | 27     | 2 (7.4%)   | 1.15 (0.27, 4.78)  | 0.852   |
| **Post surgery of upper digestive system**  | Yes | 4      | 1 (25.0%)  | 5.30 (0.59, 47.82) | 0.138   |
| **Chronic liver diseases**                  | Yes | 7      | 0 (0.0%)   | 0.76 (0.03, 16.84) | 0.861   |
| **Connective tissue diseases**              | Yes | 9      | 0 (0.0%)   | 0.59 (0.03, 12.37) | 0.735   |
| **Immunosuppression due to systemic corticosteroids or immunosuppressants** | Yes | 20 | 4 (20.0%) | 3.89 (1.16, 13.10) | 0.028   |
| **Malignancy**                              | Yes | 0      | 0 (0.0%)   | Reference        | Reference |
| **Alcoholism**                              | Yes | 2      | 1 (50.0%)  | 12.48 (0.74, 209.29) | 0.079  |
| **CKD**                                     | Yes | 0      | 0 (0.0%)   | Reference        | Reference |
| **Neurological disorders**                  | Yes | 17     | 3 (17.6%)  | 3.23 (0.86, 12.12) | 0.083   |
| **Smoking history**                         | Yes | 134    | 9 (6.7%)   | 0.70 (0.26, 1.92)  | 0.490   |
| **Long-term oxygen therapy**                | Yes | 12     | 2 (16.7%)  | 3.03 (0.65, 14.03) | 0.156   |
| **HCAP/CAP**                                | HCAP| 64     | 8 (12.5%)  | 2.45 (0.90, 6.70)  | 0.081   |
| **Performance status**                      | Unknown| 46     | 6 (13.0%)  | 2.84 (0.85, 9.47)  | 0.088   |
| **3-4**                                     | Yes | 20     | 2 (10.0%)  | 2.40 (0.48, 11.93) | 0.286   |
| **1-2**                                     | Yes | 42     | 3 (7.1%)   | 1.57 (0.39, 6.39)  | 0.528   |
| **0**                                       | Yes | 102    | 5 (4.9%)   | Reference        | Reference |
| **Charlson Comorbidity Index**              | High, Very high | 8 | 1 (12.5%) | 3.00 (0.39, 23.35) | 0.294   |
| **Medium**                                  | Yes | 115    | 10 (8.7%)  | 1.49 (0.51, 4.38)  | 0.466   |
| **Low**                                     | Yes | 87     | 5 (5.7%)   | Reference        | Reference |
| **Bacteremia**                              | Yes | 3      | 0 (0.0%)   | 1.66 (0.05, 52.69) | 0.775   |
Factors Contributing to Severe Disease and Mortality

Univariate analysis found that advanced age (≥ 65 years), neurological disorders, acute kidney injury complicated with flu-p, and pneumonia subtypes (unclassified, compared with primary viral pneumonia) were independent factors associated with severity (Table 4). Multivariate analysis found that advanced age (≥ 65 years; odds ratio [range] 2.74 [1.07-7.01]), pneumonia subtypes (unclassified, compared with primary viral pneumonia [3.31 (1.07-10.28)], diabetes mellitus (2.74 [1.01-7.46]), and acute kidney injury complicated with flu-p (14.69 [1.34-161.38]), were independent factors associated with severity. Administration of antibiotics or NI by local physicians before admission was not associated with the severity of pneumonia on admission.

A univariate analysis found that pneumonia subtypes (mixed viral and bacterial pneumonia and undifferentiated pneumonia compared with primary viral pneumonia), systemic steroids and immunosuppressant administration, complications of flu-p (pneumothorax and acute kidney injury), and severity on admission (severe) were independent factors associated with mortality (Table 5). Pneumonia subtypes (mixed viral and bacterial pneumonia [9.73 (1.48-63.96)] and undifferentiated pneumonia [14.39 (1.68-123.44)] compared with primary viral pneumonia), HCAP (3.95 [1.11-14.03]) (compared with community-acquired pneumonia), acute kidney injury complicated with flu-p (11.62 [1.28-105.10]), and severity on admission (severe) (6.39 [1.96-20.86]), were independent factors for non-survival by multivariate analysis. NI administration, number of antibiotics or concordance with the guideline, and corticosteroids administration had no significant effect on mortality.

As for mixed viral and bacterial pneumonia or secondary bacterial pneumonia, a univariate analysis found that old tuberculosis, acute kidney injury complicated with flu-p, and severity on admission (severe) were independent factors associated with mortality (Table 6). Acute kidney injury complicated with flu-p (19.71 [1.32, 294.10]) and severity on admission (severe) (7.31 [1.57, 34.04]) were independent factors for non-survival by multivariate analysis. NI administration, number of antibiotics or concordance with the guideline, and corticoste-
The age distribution, laboratory data, and complications varied in our patients with flu-p. Identified factors contributing to severity included advanced age (≥ 65 years), pneumonia subtypes (unclassified compared with primary viral pneumonia), diabetes mellitus, and acute kidney injury complicated with flu-p. Factors contributing to mortality included pneumonia subtypes (mixed viral and bacterial pneumonia and undifferentiated pneumonia compared with primary viral pneumonia), HCAP, acute kidney disease complicated with flu-p, and severity on admission (severe).

About half of our cases showed mixed viral and bacterial pneumonia or secondary bacterial pneumonia, whereas one third showed primary viral pneumonia. In the past, primary viral pneumonia in seasonal influenza was considered rare [14], but our previous study showed that 30 percent of patients with seasonal flu-p developed primary viral pneumonia. In addition, high rates of primary viral pneumonia in pH1N1 flu-p have been reported. For example, Perez-Padilla et al. [15], reported it in all 18 of their cases (100 percent), Champunot et al. [16] in 92 percent, and Cui et al. [17] in 84 percent of patients. These differences have been explained by a difference in the affinity of virus subtypes for the lung or the airways [18]. Our previous study showed a higher rate of primary viral pneumonia in patients with pH1N1 flu-p than in those with H3N2 or B flu-p [19]. Thus, it is predicted that the pattern of flu-p subtypes currently in vogue differs according to the epidemic viral subtypes year by year.

Mixed viral and bacterial pneumonia was an independent factor of mortality in this study. Bacterial pneumonia complicating influenza is well recognized as a severe manifestation of influenza; it accounted for a substantial number of deaths from the 1918 influenza pandemic [20]. Over the past decade, S. pneumoniae (29 to 48 percent) and Staphylococcus aureus (7 to 40 percent) have continued to be the dominant bacterial causes of influenza-associated bacterial pneumonia [1,21-25]. We investigated pathogens of mixed infection with flu-p with cultures, urinary antigen tests, and paired sera, and S. pneumoniae was found most frequently, followed by H. influenzae, M. pneumoniae, and C. pneumoniae. Atypical pathogens were found in 9 percent of cases. In addition, we experienced two patients with invasive aspergillosis after influenza, both of whom died. Limited cases of invasive aspergillosis with influenza have been reported [26], and the prognosis was extremely poor [27]. Aggressive investigation of the presence of fungal infection is required when physicians encounter patients with flu-p who do not respond to administered empirical antibiotics. The mechanisms by which mixed infection occur are complex: for example, virus-induced changes in the respiratory tract [28], virus-induced cytopathology and resulting immunological impairment [29], and modification of the immune response either by diminishing the ability of the host to clear bacteria or by amplification of the inflammatory cascade [30]. The results of the present study emphasized the importance of mixed infection as a prognostic factor in flu-p.

Several complications of flu-p such as pneumothorax [31] or rhabdomyolysis [32] have been reported sporadically; however, the frequency of these complications is unclear. We reviewed radiographic or computed tomography findings, laboratory data, and medical records to clarify the exact frequency of the complications. In addition, we clarified that acute kidney injury was associated with the severity and prognosis of flu-p, and thus, physicians should attempt to detect and then manage these complications appropriately.

Several of our patients with flu-p received corticosteroid therapy [33]. Some studies indicate that corticosteroids seem to have potentially harmful effects. Some of our patients with primary viral pneumonia were diagnosed initially as having acute interstitial pneumonia or cryptogenic organizing pneumonia and received corticosteroid therapy. Lung biopsy of some of these patients showed histologic patterns of organizing pneumonia or acute lung injury [19], and in some cases, the patients responded only to corticosteroid therapy, whereas antiviral agents or antibiotics failed [33]. The diagnosis of these patients was subsequently corrected to flu-p after confirming positive PCR results from samples of bronchoalveolar lavage fluid or elevated antibody titers. We hypothesize that there is a group of patients for whom corticosteroid therapy is effective, but future studies are needed to confirm this hypothesis.

Risk factors contributing to disease severity include underlying conditions known to predispose to complications from seasonal influenza, with pregnancy, obesity, and immunosuppression additionally identified [2]. The present study showed advanced age (≥ 65 years), pneumonia subtypes (undifferentiated pneumonia compared with primary viral pneumonia), diabetes mellitus, and acute kidney injury complicated with flu-p to be additional risk factors. Anamnesis was not available from some patients with a severe condition, and these patients were classified into the “unclassified” group. Therefore, it may be natural that the “unclassified” pneumonia subtype group was independently associated with severity and mortality.

We did not investigate the long-term prognosis of the patients. However, several outcome studies have been
Table 6. Univariate and multivariate analyses of factors contributing to mortality among mixed viral and bacterial pneumonia and secondary bacterial pneumonia.

|                                | N  | Mortality (%) | Univariate analysis | Multivariate analysis |
|--------------------------------|----|---------------|---------------------|-----------------------|
|                                |    |               | Odds ratio (95% CI) | P-value               |
|                                |    |               |                     |                       |
| Sex                            |    |               |                     |                       |
| Male                           | 77 | 7 (9.1%)      | 0.78 (0.20, 3.04)   | 0.715                 |
| Age 65- 59                     | 59 | 6 (10.2%)     | 1.15 (0.32, 4.13)   | 0.833                 |
| Body mass index                |    |               |                     |                       |
| Unknown                        | 41 | 7 (17.1%)     | 5.58 (0.89, 34.96)  | 0.066                 |
| ≥25                            | 10 | 2 (20.0%)     | 7.55 (0.82, 69.32)  | 0.074                 |
| 18/>                           | 15 | 0 (0.0%)      | 0.83 (0.03, 23.48)  | 0.912                 |
| 25>BMI≥18                      | 39 | 1 (2.6%)      | 7.55 (0.82, 69.32)  | 0.074                 |
| Vaccination history            |    |               |                     |                       |
| 23-valent pneumococcal         |    |               |                     |                       |
| polysaccharide                 |    |               |                     |                       |
| Unknown                        | 1  | 0 (0.0%)      |                     |                       |
| No                             | 101| 10 (9.9%)     | 0.80 (0.02, 26.10)  | 0.902                 |
| Influenza vaccination          |    |               |                     |                       |
| within one year                |    |               |                     |                       |
| Unknown                        | 29 | 1 (3.4%)      | 0.58 (0.05, 6.36)   | 0.655                 |
| No                             | 59 | 8 (13.6%)     | 1.82 (0.28, 11.77)  | 0.532                 |
| Prior antibiotic treatment     |    |               |                     |                       |
| No                             | 67 | 4 (6.0%)      | 0.35 (0.10, 1.28)   | 0.114                 |
| Viral subtype                  |    |               |                     |                       |
| A/H1N1 seasonal                | 5  | 0 (0.0%)      | 1.61 (0.04, 58.00)  | 0.796                 |
| pH1N1                          | 7  | 1 (14.3%)     | 4.08 (0.32, 51.24)  | 0.277                 |
| A/Undifferentiated             | 43 | 6 (14.0%)     | 3.06 (0.47, 19.97)  | 0.242                 |
| B                              | 23 | 2 (8.7%)      | 2.05 (0.24, 17.53)  | 0.510                 |
| A/H3N2                         | 27 | 1 (3.7%)      | Reference           | Reference             |
| Comorbidities                  |    |               |                     |                       |
| Chronic pulmonary diseases     |    |               |                     |                       |
| Yes                            | 48 | 5 (10.4%)     | 1.21 (0.34, 4.26)   | 0.770                 |
| COPD                           |    |               |                     |                       |
| Yes                            | 26 | 1 (3.8%)      | 0.44 (0.07, 2.67)   | 0.370                 |
| Asthma                         |    |               |                     |                       |
| Yes                            | 6  | 0 (0.0%)      | 0.66 (0.03, 15.65)  | 0.794                 |
| Bronchiectasis                 |    |               |                     |                       |
| Yes                            | 8  | 1 (12.5%)     | 1.86 (0.26, 13.46)  | 0.537                 |
| Pulmonary NTM                  |    |               |                     |                       |
| Yes                            | 3  | 0 (0.0%)      | 1.26 (0.04, 40.90)  | 0.897                 |
| Old tuberculosis               |    |               |                     |                       |
| Yes                            | 6  | 3 (50.0%)     | 12.33 (2.11, 72.16) | 0.005                 |
| Interstitial pneumonia         |    |               |                     |                       |
| Yes                            | 6  | 0 (0.0%)      | 0.66 (0.03, 15.65)  | 0.794                 |
| Hypertension                   |    |               |                     |                       |
| Yes                            | 14 | 1 (7.1%)      | 0.97 (0.15, 6.27)   | 0.970                 |
Table 6, cont’d. Univariate and multivariate analyses of factors contributing to mortality among mixed viral and bacterial pneumonia and secondary bacterial pneumonia.

| Factor                                                   | Yes | No   | Yes % | No % | χ²     | p     |
|----------------------------------------------------------|-----|------|-------|------|--------|-------|
| Chronic cardiac diseases                                 | 11  | 2    | 18.2% |      | 2.68   | 0.233 |
| Congestive heart failure                                 | 4   | 1    | 25.0% |      | 4.17   | 0.212 |
| Ischemic heart diseases                                  | 7   | 1    | 14.3% |      | 2.17   | 0.450 |
| Arrhythmias                                              | 2   | 0    | 0.0%  |      | 1.78   | 0.765 |
| Diabetes mellitus                                        | 15  | 2    | 13.3% |      | 1.80   | 0.462 |
| Post surgery of upper digestive system                   | 2   | 1    | 50.0% |      | 9.94   | 0.114 |
| Chronic liver diseases                                   | 4   | 0    | 0.0%  |      | 0.97   | 0.985 |
| Connective tissue diseases                               | 6   | 0    | 0.0%  |      | 0.66   | 0.794 |
| Immunosuppression due to systemic corticosteroids or immunosuppressants | 13  | 2    | 15.4% |      | 2.16   | 0.341 |
| Malignancy                                               | 0   | 0    | 0.0%  |      |        |       |
| Alcoholism                                               | 2   | 1    | 50.0% |      | 9.94   | 0.114 |
| CKD                                                      | 0   | 0    | 0.0%  |      |        |       |
| Neurological disorders                                   | 8   | 0    | 0.0%  |      | 0.49   | 0.651 |
| Smoking history                                          | 68  | 6    | 8.8%  |      | 0.77   | 0.697 |
| Long-term oxygen therapy                                 | 4   | 0    | 0.0%  |      | 0.97   | 0.985 |
| HCAP/CAP                                                 | 29  | 4    | 13.8% |      | 1.91   | 0.328 |
| Performance status                                       | 16  | 2    | 12.5% |      | 1.55   | 0.600 |
| 3-4                                                      | 11  | 1    | 9.1%  |      | 1.29   | 0.805 |
| 1-2                                                      | 24  | 2    | 8.3%  |      | 1.00   | 1.000 |
| 0                                                       | 54  | 5    | 9.3%  |      |        |       |
| Charlson Comorbidity Index                               | 1   | 0    | 0.0%  |      | 3.15   | 0.620 |
| High, Very high                                          | 62  | 6    | 9.7%  |      | 0.98   | 0.980 |
| Medium                                                   | 42  | 4    | 9.5%  |      | 1.26   | 0.897 |
| Bacteremia                                               | 3   | 0    | 0.0%  |      |        |       |
| Complications                                            |     |      |       |      |        |       |
| Pneumothorax                                             | 1   | 1    | 100.0%|      |        |       |
| Pleuritis or pyothorax                                   | 2   | 1    | 50.0% |      | 9.94   | 0.114 |
| Acute kidney disease                                     | 5   | 4    | 80.0% |      | 43.62  | <.001 |
|                                          |     |      |       |      | 20.72  | 0.024 |
|                                          |     |      |       |      | (1.49, 288.51) |        |
conducted, and the mortality rates among the patients who survived the initial event of pneumonia were substantially higher than those in the control subjects [34-37]. This is thought to be associated with the increased incidence of pulmonary or cardiovascular complications. Furthermore, patients with more severe pneumonia have a higher risk of long-term mortality than patients with less severe pneumonia [34]. These findings suggest that the factors associated with severe pneumonia are also important in predicting prognosis after hospital discharge. Efforts to improve the prevention and management of pneumonia, especially in severe cases, are clearly necessary and may reduce the rate of long-term mortality.

The mortality rate of patients with flu-p in the present study was 7.6 percent, which is consistent with that reported in previous studies of 5.5 percent [38] to 29.4 percent [21]. Previous studies have suggested the following as prognostic factors: advanced age, Caucasian race, nursing home resident, chronic lung disease, cardiovascular disease, renal disease, immunosuppression, obesity, and lymphopenia not resolved after 5 days of treatment [2,4]. We identified the following additional prognostic factors: pneumonia subtypes, HCAP, acute kidney injury complicated with flu-p, and severity on admission. Our results suggest the importance of classifying pneumonia and identifying complications of flu-p and disease severity on admission. Unclassified pneumonia subtype was independently associated with severity, and both this subtype and severe pneumonia as evaluated by ATS/IDSA severity criteria were prognostic factors of flu-p. Although the exact reason is unknown, this result may indicate that patients with unclassified pneumonia subtype had some factors that were not included in the ATS/IDSA severity criteria. We also found HCAP to be an independent prognostic factor. HCAP describes a patient population with frequent healthcare contacts that is not only at high risk of contracting resistant organisms but also elderly and frail. We previously reported that flu-p is the second leading cause of HCAP [8], but to our knowledge, only a few reports have investigated influenza virus in HCAP. The frequency of flu-p may be underestimated, and the results obtained in the present study suggest that flu-p is important in the patient population with HCAP.

The use of antibiotics or NI was not associated with the severity of pneumonia or mortality in this study although numerous reports have shown positive results with antibiotics or NI for pneumonia [39,40]. We initially suspected the complexity of flu-p as a possible cause of this result. Flu-p can be classified into four types: primary viral pneumonia, secondary bacterial pneumonia, mixed viral and bacterial pneumonia, and unclassified subtype. For patients with secondary bacterial pneumonia and mixed viral and bacterial pneumonia, the significance of antibiotics is theoretically increased, whereas it is assumed that antibiotics have little effect on primary viral pneumonia. Therefore, we further analyzed the effect of concordant antibiotics therapy on patient outcome in the mixed viral and bacterial pneumonia and secondary bacterial pneumonia subtypes; however, no favorable effect of concordant antibiotics therapy on outcome was
found. Two reasons are suggested for these results: first, the number of patients in the present study was small. There were only 16 non-survivors, and a limited number of prognostic factors could be identified statistically. Second, the frequency of atypical pathogens in mixed viral and bacterial or secondary infection was relatively lower than that in previous reports of CAP [7,41]. Atypical pathogens were present in 9 percent of our flu-p patients and in only 2 of the non-survivors. Most of the patients receiving guideline-discordant treatment were treated with single β-lactams, and most pathogens in the mixed viral and bacterial or secondary bacterial pneumonias were covered. This may be a reason why guideline-concordant therapy had little effect on patient outcome in the present study.

This study has several limitations. We could collect data from medical records only from December 1999 through March 2016; thus, the numbers of patients included in both 1999 and 2016 are limited. Because this is a nonrandomized observational study, the level of confidence in the results is lessened, and a complete diagnostic workup to determine etiology was not possible in every patient. Further, RT-PCR was performed only in a limited number of patients. To assess factors related to severity and prognosis, we selected factors associated with patient demographics, complications, and those of CAP/HCAP or flu-p identified in previous studies for univariate and multivariate analysis. Several profiles of immune cells or cytokines have been identified as key factors of flu-p in recent studies [42-45], but we could not assess the significance of these factors because of the retrospective nature of the present study. Finally, this was a single-center study, and the results may not be applicable in other settings.

In conclusion, flu-p presents a variety of clinical features. We identified characteristics of flu-p and factors contributing to the severity of and mortality from flu-p. Knowledge of patient profiles and underlying diseases, mixed infections and complications, and identification of disease severity on admission are required for the adequate management of flu-p.

Acknowledgements: We thank Yuri Baba, Masaki Tamura, and Shozaburo Yamaguchi at the Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, for their detailed comments regarding the present study.

REFERENCES

1. Garg S, Jain S, Dawood FS, Jung M, Pérez A, D’Mello T, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection—United States, 2005-2008. BMC Infect Dis. 2015;15:369–377. 2. CDC home. Past weekly surveillance reports. Cited 2016. Jul 7. Available from: http://www.cdc.gov/flu/weekly/pastreports.htm.

3. Maruyama T, Fujisawa T, Suga S, Nakamura H, Nagao M, Taniguchi K, et al. Outcomes and prognostic features of patients with influenza requiring hospitalization and receiving early antiviral therapy: a prospective multicenter-cohort study. Chest. 2016;149:526–534.

4. Cui W, Zhao H, Lu X, Wen Y, Zhou Y, Deng B, et al. Factors associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China. BMC Infect Dis. 2010;10:145–153.

5. Olken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–655.

6. American Thoracic Society; Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.

7. Ishiguro T, Takayanagi, N, Yamaguchi S, Yamakawa H, Nakamoto K, Takaku Y, et al. Etiology and factors contributing to the severity and mortality of community-acquired pneumonia. Intern Med. 2013;52(3):317–324.

8. Ishiguro T, Takayanagi N, Gochi M, Takaku Y, Kagiyma N, Kurashima K, et al. Etiology and factors contributing to mortality in healthcare-associated pneumonia: a single-center study. Showa Univ J Med Sci. 2013;25(4):263–275.

9. Louria DB, Blumenfeld HL, Ellis JT, Kilbourne ED, Rogers DE. Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. J Clin Invest. 1959;3(1 Part 2):213–265.

d. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med. 2010;38(4):e91–97.

12. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1. doi:10.1038/kisup.2012.1.

13. Heinz G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002;21(16):2409–2419.

14. Trenor JJ. Influenza viruses, including avian influenza and swine influenza. In: Mandell G, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases. Seventh edition. Philadelphia, PA: Churchill Livingstone; 2010. pp. 2265–2289.

15. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, et al. Pneumonia and respiratory failure from swine-origin influenza (H1N1) in Mexico. N Engl J Med. 2009;361(7):680–689.

16. Champunot R, Tanjathan S, Kerdsin A, Puangpatra P, Hernandez M, Quiñones-Falconi F, Bautista E, et al. Impact of pandemic influenza (H1N1) virus-associated community-acquired pneumonia among adults in a tertiary hospital in Thailand. Jpn J Infect Dis. 2010;63(4):251–256.

17. Cui W, Zhao H, Lu X, Wen Y, Zhou Y, Deng B, et al. Factors
associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China. J Infect Dis. 2010;10:145–153.
18. Itoh Y, Shinya K, Kiso M, Watanabe T, Sakoda Y, Hatta M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature. 2009;460(7258):1021–1025.
19. Ishiguro T, Takayanagi N, Kanauchi T, Uozumi R, Kawate T, Takaku Y, et al. Clinical and radiographic comparison of influenza virus-associated pneumonia among three viral subtypes. Intern Med. 2016;55(7):731–737.
20. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008;198(7):962–970.
21. Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. Chest. 2001;119(6):1717–1723.
22. Chang YS, van Hal SJ, Spencer PM, Gossell IB, Collett PW. Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the “PROTECT” phase of the pandemic response. Med J Aust. 2010;192(2):90–93.
23. Scadding JG. Lung changes in influenza. Q J Med. 1937;6:425–465.
24. Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. Lancet Infect Dis. 2006;6(5):303–312.
25. Petersdorf RG, Fusco JJ, Harter DH, Albrink WS. Pulmonary infections complicating Asian influenza. AMA Arch Intern Med. 1959;103(2):262–272.
26. Wauters J, Baar I, Meersseman P, Meersseman W, Dams K, De Paep R, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med. 2012;38(11):1761–1768.
27. Matsushima H, Takayanagi N, Ubukata M, Sugita Y, Kanazawa M, Kawabata Y. Invasive pulmonary aspergillosis following influenza A infection. Nihon Kokyu Gakkai Zasshi. 2001;39(9):672–677. [in Japanese]
28. Beadling C, Silika MK. How do viral infections predispose patients to bacterial infections? Curr Opin Infect Dis. 2004;17(3):185–191.
29. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev. 2006;19(3):571–582.
30. Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. Influenza Other Respir Viruses. 2013;7(Suppl 2):105–113.
31. Guo HH, Sweeney RT, Regula D, Leung AN. Fatal 2009 influenza A (H1N1) infection, complicated by acute respiratory distress syndrome and pulmonary interstitial emphysema. Radiographics. 2010;30(2):327–333.
32. Fadila MF, Wool KJ. Rhabdomyolysis secondary to influenza A infection: a case report and review of the literature. N Am J Med Sci. 2015;7(3):114–117.
33. Ishiguro T, Takayanagi N, Kanauchi T, Hoshi T, Yanagisawa T, Sugita Y. [Two patients with novel influenza A virus (H1N1) pneumonia treated with steroid therapy after an incorrect diagnosis of rapid progressive interstitial pneumonia due to the negative results of a rapid-antigen test]. Nihon Kokyu Gakkai Zasshi. 2010;48(9):687–695. [in Japanese]
34. Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Ten-year mortality after community-acquired pneumonia: a prospective cohort. Am J Respir Crit Care Med. 2015;192(5):597–604.
35. Campbell SG, Patrick W, Urquhart DG, Maxwell DM, Ackroyd-Stolarz SA, Murray DD, et al. Patient with community-acquired pneumonia discharged from the emergency department according to a clinical practice guideline. Emerg Med J. 2004;21(6):667–669.
36. Minogue MF, Coley CM, Fine MJ, Marrie TJ, Kapoor WN, Singer DE. Patients hospitalized after initial outpatient treatment for community-acquired pneumonia. Ann Emerg Med. 1998;31(3):376–380.
37. Labarere J, Stone RA, Obrosky DS, Yealy DM, Meehan TP, Fine JM, et al. Comparison of outcomes for low-risk outpatients and inpatients with pneumonia: a propensity-adjusted analysis. Chest. 2007;131(2):480–488.
38. Riquelme R, Torres A, Rioseco ML, Ewig S, Cillóniz C, Riquelme M, et al. Influenza pneumonia: a comparison between seasonal influenza virus and the H1N1 pandemic. Eur Respir J. 2011;38(1):106–111.
39. McCullers JA. Effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza. J Infect Dis. 2004;190(3):519–526.
40. Lee N, Choi KW, Chan PK, Hui DS, Lui GC, Wong BC, et al. Outcomes of adults hospitalized with severe influenza. Thorax. 2010;65:510–515.
41. Herrero FS, Olivas JB. Microbiology and risk factors for community-acquired pneumonia. Semin Respir Crit Care Med. 2012;33:220–231.
42. Jamieson AM, Yu S, Annicelli CH, Medzhitov R. Influenza-virus-induced glucocorticoids compromise innate host defense against a secondary bacterial infection. Cell Host Microbe. 2010;7(2):103–114.
43. Jamieson AM, Pasman L, Yu S, Gamradt P, Homer RJ, Decker T, et al. Role of tissue protection in lethal respiratory viral-bacterial coinfection. Science. 2013;340(6137):1230–1234.
44. Kash JC, Tupney TM, Proll SC, Carter V, Perwitasari O, Thomas MJ, et al. Genomic analysis of increased host immune defense against a secondary bacterial infection. Cell Host Microbe. 2010;7(2):103–114.
45. Oshansky CM, Gartland AJ, Wong SS, Jeevan T, Wang D, Roddam PL, et al. Mucosal Immune response predicts clinical outcomes during influenza infection independently of age and viral load. Am J Respir Crit Care Med. 2014;189(4):449–46.