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ORIGINAL CONTRIBUTION

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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

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†Abbreviations: *flu-p*, influenza-associated pneumonia; HCAP, healthcare-associated pneumonia; CAP, community-acquired pneumonia; NI, neuraminidase inhibitors; PS, performance status; RT-PCR, reverse transcription polymerase chain reaction; COPD, chronic obstructive pulmonary disease.

Keywords: influenza associated pneumonia, severity, prognosis, prognostic factor, outcome

Author contributions: T. I. is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. N. T., N. K., Y. T., and K. K. aggregated the data, created the tables, and helped draft the discussion of the manuscript. R. U. and S. M. performed the statistical analysis.

Table 1. Patient Characteristics.

Characteristic	Total	Primary viral pneumonia	Mixed viral and bacterial pneumonia	Secondary pneumonia	Unclassified	*P*-value
		N = 76	N = 71	N = 34	N = 29	
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 (17.6%)	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 aspergillosis	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

Table 1, cont'd. Patient Characteristics.

Arrhythmia	6 (2.9%)	3 (3.9%)	1 (1.4%)	1 (2.9%)	1 (3.4%)	0.825
Diabetes mellitus	27 (12.9%)	9 (11.8%)	13 (18.3%)	2 (5.9%)	3 (10.3%)	0.309
Post surgery of upper digestive system	4 (1.9%)	2 (2.6%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	0.625
Chronic liver disease	7 (3.3%)	2 (2.6%)	2 (2.8%)	2 (5.9%)	1 (3.4%)	0.835
Connective tissue disease	9 (4.3%)	3 (3.9%)	4 (5.6%)	2 (5.9%)	0 (0.0%)	0.605
Psychiatric disease	6 (2.9%)	2 (2.6%)	3 (4.2%)	0 (0.0%)	1 (3.4%)	0.676
Malignancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Alcoholism	2 (1.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	0.267
Steroid or immunosuppressant use	20 (9.5%)	6 (7.9%)	8 (11.3%)	5 (14.7%)	1 (3.4%)	0.426
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Neurological disorders	17 (8.1%)	5 (6.6%)	8 (11.3%)	0 (0.0%)	4 (13.8%)	0.141
Laboratory data						
WBC	11202.4 ± 6339.69	10382.9 ± 5636.04	12069.0 ± 7507.49	11985.3 ± 5005.10	10310.3 ± 6260.33	0.298
AST	57.8 ± 169.89	77.8 ± 273.60	53.2 ± 61.10	38.6 ± 39.35	39.1 ± 30.75	0.599
LDH	334.1 ± 406.36	397.0 ± 641.92	312.9 ± 155.89	285.9 ± 174.42	277.0 ± 95.35	0.384
BUN	21.5 ± 17.29	18.7 ± 11.03	26.3 ± 24.82	15.8 ± 6.93	22.9 ± 11.76	0.015
Cre	0.9 ± 0.44	0.9 ± 0.32	1.0 ± 0.61	0.7 ± 0.24	0.9 ± 0.33	0.030
CRP	14.0 ± 10.33	11.8 ± 8.24	18.0 ± 12.14	14.8 ± 10.09	9.4 ± 7.06	<.001
Complications						
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.

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 2. Diagnostic methods and patient results (*n* = 210).

Method	No. of episodes studied	No. of positive diagnostic studies (%)	
		Other than influenza virus	Influenza virus
Paired sera	157	13	82
Rapid influenza diagnostic test	208	-	154
RT-PCR	12	-	12
Urinary antigen			
Streptococcus pneumoniae	178	48	-
Legionella sp.	178	2	-
Culture			
Sputum	176	41	-
Transbronchial aspirate	10	2	-
Protected specimen brush	2	0	-
Bronchial washing	3	0	-
Bronchoalveolar lavage fluid	16	2	-
Blood	140	3	-
Pleural fluid	3	0	-

RT-PCR, reverse-transcription polymerase chain reaction.

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

Table 3. Mixed infection with influenza virus.

Pathogens	Total *n*	% of 210 patients -	Severe *n*	Non-survivors *n*
Two pathogens				
Streptococcus pneumoniae + *Chlamydophila 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	0	0
S. pneumoniae + *Aspergillus fumigatus*	1	0.5	1	1
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/m^2 in 22 patients and < 18 kg/m^2 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.

				Univariate analysis		Multivariate analysis	
		N	Severe (%)	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 polysaccharide vaccination within 5 years	Unknown	2	0 (0.0%)				
	No	201	54 (26.9%)	0.92 (0.17, 4.87)	0.920		
	Yes	7	2 (28.6%)				
Influenza vaccination within one year	Unknown	50	11 (22.0%)	0.81 (0.28, 2.31)	0.695		
	No	129	37 (28.7%)	1.16 (0.47, 2.82)	0.749		
	Yes	31	8 (25.8%)	Reference			
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
	Primary viral	76	17 (22.4%)	Reference		Reference	
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.

Comorbidities							
Chronic pulmonary diseases	Yes	95	25 (26.3%)	0.97 (0.52, 1.79)	0.917	0.92 (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, 7.46)	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, 8.49)	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, 6.24)	0.095
	PS 3-4	20	6 (30.0%)	2.00 (0.68, 5.91)	0.210	0.68 (0.16, 2.85)	0.600
	PS 1-2	42	11 (26.2%)	1.66 (0.70, 3.90)	0.248	1.20 (0.43, 3.35)	0.734
	PS 0	102	18 (17.6%)	Reference		Reference	
Charlson Comorbidity Index	High, Very high	8	3 (37.5%)	2.01 (0.44, 9.16)	0.367		

Table 4, cont'd. Univariate and multivariate analyses of factors contributing to severe pneumonia.

	Medium	115	33 (28.7%)	1.35 (0.71, 2.56)	0.362		
	Low	87	20 (23.0%)	Reference			
Bacteremia	Yes	3	1 (33.3%)	1.38 (0.12, 15.54)	0.793		
Complications							
Pneumothorax	Yes	4	3 (75.0%)	8.66 (0.88, 85.01)	0.064		
Pleuritis or pyothorax	Yes	2	1 (50.0%)	2.78 (0.17, 45.20)	0.473		
Acute kidney disease	Yes	7	6 (85.7%)	19.69 (3.98, 97.49)	<0.001	14.69 (1.34, 161.38)	0.028
Acute pulmonary thromboembolism	Yes	2	0 (0.0%)				
Myocarditis	Yes	2	2 (100.0%)				
Neurological symptoms (encephalitis, meningitis)	Yes	7	3 (42.9%)	2.12 (0.46, 9.80)	0.334		
Rhabdomyolysis	Yes	13	7 (53.8%)	1.41 (0.23, 8.83)	0.711	3.16 (0.82, 12.14)	0.094

CAP, community-acquired pneumonia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NTM, nontuberculous mycobacteriosis.

Methods used to identify the etiology of pneumonia are shown in Table 2. The most common microorganism in mixed infection was *S. pneumoniae*, and other microorganisms included *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and others. Etiologies of mixed or secondary infection both in patients with severe disease and in non-survivors are listed in Table 3.

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).

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

Table 5. Univariate and multivariate analyses of factors contributing to mortality.

				Univariate analysis		Multivariate analysis	
		N	Mortality (%)	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	1.38 (0.31, 6.11)	0.668
	≥25	22	2 (9.1%)	3.68 (0.58, 23.34)	0.167	2.26 (0.31, 16.42)	0.420
	18>	33	2 (6.1%)	2.40 (0.39, 14.80)	0.347	0.54 (0.07, 4.40)	0.566
	25>BMI≥18	77	2 (2.6%)	Reference		Reference	
23-valent pneumococcal polysaccharide vaccination within 5 years	Unknown	2	0 (0.0%)	3.00 (0.02, 370.45)	0.655		
	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	9.73 (1.48, 63.96)	0.018
	Secondary bacterial	34	2 (5.9%)	3.87 (0.48, 31.17)	0.203	8.88 (0.90, 87.99)	0.062
	Unclassified	29	5 (17.2%)	11.30 (1.73, 73.99)	0.011	14.39 (1.68, 123.44)	0.015
	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	2.97 (0.11, 82.97)	0.521
	pH1N1	23	1 (4.3%)	2.11 (0.20, 22.25)	0.534	9.77 (0.65, 147.70)	0.100
	A/Undifferentiated	85	11 (12.9%)	4.89 (0.84, 28.32)	0.077	4.16 (0.63, 27.60)	0.140
	B	46	3 (6.5%)	2.55 (0.35, 18.39)	0.354	2.18 (0.26, 18.18)	0.470
	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		

Table 5 cont'd. Univariate and multivariate analyses of factors contributing to mortality.

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		
Arrythmias	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%)				
Alcoholism	Yes	2	1 (50.0%)	12.48 (0.74, 209.29)	0.079		
CKD	Yes	0	0 (0.0%)				
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	3.95 (1.11, 14.03)	0.033
Performance status	Unknown	46	6 (13.0%)	2.84 (0.85, 9.47)	0.088	1.30 (0.27, 6.37)	0.744
	3-4	20	2 (10.0%)	2.40 (0.48, 11.93)	0.286	0.75 (0.09, 6.26)	0.794
	1-2	42	3 (7.1%)	1.57 (0.39, 6.39)	0.528	0.71 (0.13, 3.95)	0.691
	0	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	115	10 (8.7%)	1.49 (0.51, 4.38)	0.466		
	Low	87	5 (5.7%)	Reference			
Bacteremia	Yes	3	0 (0.0%)	1.66 (0.05, 52.69)	0.775		

Table 5 cont'd. Univariate and multivariate analyses of factors contributing to mortality.

Complications							
Pneumothorax	Yes	4	2 (50.0%)	13.27 (1.74, 101.23)	0.013		
Pleuritis or pyothorax	Yes	2	1 (50.0%)	12.48 (0.74, 209.29)	0.079		
Acute kidney disease	Yes	7	4 (57.1%)	19.69 (3.98, 97.49)	<.001	11.62 (1.28, 105.10)	0.029
Acute pulmonary thromboembolism	Yes	2	0 (0.0%)	2.33 (0.05, 99.51)	0.658		
Myocarditis	Yes	2	0 (0.0%)	2.33 (0.05, 99.51)	0.658		
Neurological symptoms (encephalitis, meningitis)	Yes	7	1 (14.3%)	2.81 (0.39, 20.08)	0.304		
Rhabdomyolysis	Yes	13	1 (7.7%)	1.41 (0.23, 8.83)	0.711		
Severity	Severe	56	13 (23.2%)	13.43 (3.93, 45.90)	<.001	6.39 (1.96, 20.86)	0.002
Concordance with CAP guideline-recommended treatment	Discordant	74	7 (9.5%)	1.49 (0.54, 4.08)	0.437		
Number of initial antibiotics	≥2	135	9 (6.7%)	0.69 (0.25, 1.88)	0.463		
Neuraminidase inhibitors	No	53	3 (5.7%)	0.51 (0.14, 1.79)	0.293		
	≥48 h	62	2 (3.2%)	0.30 (0.07, 1.25)	0.099		
	<48 h	95	1+E4:E691 (11.6%)	Reference			

CAP, community-acquired pneumonia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NTM, nontuberculous mycobacteriosis.

mortality (17.2 percent).

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-

roids administration had no significant effect on mortality.

DISCUSSION

We focused on clinical features and factors contributing to the severity and mortality of *flu-p* in this study. 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.

				Univariate analysis		Multivariate analysis	
		N	Mortality (%)	Odds ratio (95 % CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Sex	Male	77	7 (9.1%)	0.78 (0.20, 3.04)	0.715		
Age	65-	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	2.44 (0.34, 17.59)	0.375
	≥25	10	2 (20.0%)	7.55 (0.82, 69.32)	0.074	3.17 (0.26, 38.63)	0.366
	18>	15	0 (0.0%)	0.83 (0.03, 23.48)	0.912	0.92 (0.04, 21.50)	0.957
	25>BMI≥18	39	1 (2.6%)			Reference	
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	3.67 (0.08, 162.70)	0.502
	pH1N1	7	1 (14.3%)	4.08 (0.32, 51.24)	0.277	12.00 (0.60, 239.34)	0.104
	A/Undifferentiated	43	6 (14.0%)	3.06 (0.47, 19.97)	0.242	2.47 (0.30, 20.32)	0.399
	B	23	2 (8.7%)	2.05 (0.24, 17.53)	0.510	3.69 (0.38, 35.61)	0.259
	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	3.18 (0.64, 15.87)	0.158
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.

Chronic cardiac diseases	Yes	11	2 (18.2%)	2.68 (0.53, 13.51)	0.233		
Congestive heart failure	Yes	4	1 (25.0%)	4.17 (0.44, 39.24)	0.212		
Ischemic heart diseases	Yes	7	1 (14.3%)	2.17 (0.29, 16.28)	0.450		
Arrythmias	Yes	2	0 (0.0%)	1.78 (0.04, 77.55)	0.765		
Diabetes mellitus	Yes	15	2 (13.3%)	1.80 (0.38, 8.59)	0.462		
Post surgery of upper digestive system	Yes	2	1 (50.0%)	9.94 (0.57, 172.22)	0.114		
Chronic liver diseases	Yes	4	0 (0.0%)	0.97 (0.03, 27.03)	0.985		
Connective tissue diseases	Yes	6	0 (0.0%)	0.66 (0.03, 15.65)	0.794		
Immunosuppression due to systemic corticosteroids or immunosuppressants	Yes	13	2 (15.4%)	2.16 (0.44, 10.56)	0.341		
Malignancy	Yes	0	0 (0.0%)				
Alcoholism	Yes	2	1 (50.0%)	9.94 (0.57, 172.22)	0.114		
CKD	Yes	0	0 (0.0%)				
Neurological disorders	Yes	8	0 (0.0%)	0.49 (0.02, 10.80)	0.651		
Smoking history	Yes	68	6 (8.8%)	0.77 (0.21, 2.80)	0.697		
Long-term oxygen therapy	Yes	4	0 (0.0%)	0.97 (0.03, 27.03)	0.985		
HCAP/CAP	HCAP	29	4 (13.8%)	1.91 (0.52, 7.03)	0.328	4.41 (0.64, 30.30)	0.131
Performance status	Unknown	16	2 (12.5%)	1.55 (0.30, 8.04)	0.600	0.46 (0.04, 4.72)	0.511
	3-4	11	1 (9.1%)	1.29 (0.17, 9.46)	0.805	0.12 (0.00, 3.36)	0.212
	1-2	24	2 (8.3%)	1.00 (0.20, 4.97)	1.000	0.59 (0.07, 4.62)	0.613
	0	54	5 (9.3%)	Reference		Reference	
Charlson Comorbidity Index	High, Very high	1	0 (0.0%)	3.15 (0.03, 291.68)	0.620		
	Medium	62	6 (9.7%)	0.98 (0.27, 3.55)	0.980		
	Low	42	4 (9.5%)	Reference			
Bacteremia	Yes	3	0 (0.0%)	1.26 (0.04, 40.90)	0.897		
Complications							
Pneumothorax	Yes	1	1 (100.0%)				
Pleuritis or pyothorax	Yes	2	1 (50.0%)	9.94 (0.57, 172.22)	0.114		
Acute kidney disease	Yes	5	4 (80.0%)	43.62 (4.95, 384.39)	<.001	20.72 (1.49, 288.51)	0.024

Table 6, cont'd. Univariate and multivariate analyses of factors contributing to mortality among mixed viral and bacterial pneumonia and secondary bacterial pneumonia.

Acute pulmonary thromboembolism	Yes	0	0 (0.0%)				
Myocarditis	Yes	1	0 (0.0%)	2.98 (0.03, 290.36)	0.641		
Neurological symptoms (encephalitis, meningitis)	Yes	2	1 (50.0%)	9.94 (0.57, 172.22)	0.114		
Rhabdomyolysis	Yes	7	1 (14.3%)	2.17 (0.29, 16.28)	0.450		
Severity	Severe	26	8 (30.8%)	14.24 (3.13, 64.71)	<.001	8.07 (1.66, 39.22)	0.010
Concordance with CAP guideline-recommended treatment	Discordant	38	5 (13.2%)	1.87 (0.53, 6.62)	0.335	1.63 (0.29, 9.20)	0.578
Number of initial antibiotics	≥2 drugs	66	6 (9.1%)	0.85 (0.23, 3.06)	0.801		
Neuraminidase inhibitors	No	20	2 (10.0%)	0.84 (0.18, 3.99)	0.824		
	≥48 h	32	1 (3.1%)	0.30 (0.05, 1.85)	0.193		
	<48 h	53	7 (13.2%)	Reference			

CAP, community-acquired pneumonia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NTM, nontuberculous mycobacteriosis.

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*.

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