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MAJOR ARTICLE

Factors Associated With the Development of Bacterial Pneumonia Related to Seasonal Influenza Virus Infection: A Study Using a Large-scale Health Insurance Claim Database

Masahiro Shirata,[1,©] Isao Ito,[1] Taisuke Jo,[2,3] Tomohide Iwao,[4] Issei Oi,[1] Nobuyoshi Hamao,[1] Kensuke Nishioka,[1] Hayato Yamana,[2] Takahide Nagase,[3] Hideo Yasunaga,[5] and Toyohiro Hirai[1]

[1]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [4]Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital, Kyoto, Japan, and [5]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan

Background. Influenza-related bacterial pneumonia is a leading complication of influenza infection. However, the differences in the incidence rates and risk factors associated with concomitant viral/bacterial pneumonia (CP) and secondary bacterial pneumonia following influenza (SP) remain unclear. This study aimed to clarify the incidence rates of CP and SP following seasonal influenza and identify factors associated with their development.

Methods. This retrospective cohort study was conducted using the JMDC Claims Database, a health insurance claims database in Japan. All patients aged <75 years who developed influenza during 2 consecutive epidemic seasons, 2017/2018 and 2018/2019, were analyzed. CP was defined as bacterial pneumonia diagnosed between 3 days before and 6 days after the date of influenza diagnosis, and SP was defined as pneumonia diagnosed 7–30 days after the date of diagnosis. Multivariable logistic regression analyses were performed to identify factors associated with the development of CP and SP.

Results. Among the 10 473 014 individuals registered in the database, 1 341 355 patients with influenza were analyzed. The average age at diagnosis (SD) was 26.6 (18.6) years. There were 2901 (0.22%) and 1262 (0.09%) patients who developed CP and SP, respectively. Age 65–74 years, asthma, chronic bronchitis/emphysema, cardiovascular disease, renal disease, malignant tumor, and immunosuppression were significant risk factors for both CP and SP, whereas cerebrovascular disease, neurological disease, liver disease, and diabetes were risk factors specific to CP development.

Conclusions. The results determined the incidence rates of CP and SP and identified their risk factors, such as older age and comorbidities.

Keywords. seasonal influenza; bacterial pneumonia; database; risk factor.

Influenza remains a major public health concern worldwide, with an estimated 1 billion cases and 1 million deaths annually [1]. Influenza-associated pneumonia is the leading complication of seasonal and pandemic influenza and increases the risk of respiratory failure and death in adults and children [2–7]. The incidence of influenza-associated pneumonia ranges from 0.1% to ≥10%, depending on the levels of antigenic variation and virulence of circulating strains [8].

Influenza-associated pneumonia is classified into primary viral pneumonia (primary pneumonia), combined viral and bacterial pneumonia (concomitant pneumonia [CP]), and secondary bacterial pneumonia following influenza (secondary pneumonia [SP]) [9]. Primary pneumonia is considered rare, especially during the interpandemic period [10]. In contrast, bacterial co-/superinfection represented by bacterial pneumonia is a major cause of mortality in patients with seasonal and pandemic influenza [11, 12]. Several pathological studies have reported that the majority of victims during the 1918/1919 and 1957/1958 pandemics had complications due to bacterial pneumonia [9, 13, 14]. Bacterial coinfections were also identified in 26%–55% of autopsy respiratory specimens from the 2009 pandemic influenza A (H1N1) virus infection [15, 16].

Multifactorial processes of bacterial pneumonia, which differ between the early and late phases after influenza infection, have been suggested [17]. Age and underlying diseases such as asthma

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Correspondence: Isao Ito, MD, PhD, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo, Kyoto 606-8507, Japan (isaoito@kuhp.kyoto-u.ac.jp); or Masahiro Shirata, MD, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo, Kyoto 606-8507, Japan (mshirata@kuhp.kyoto-u.ac.jp).

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and cardiovascular disease are risk factors associated with the development of pneumonia in patients with seasonal influenza [3, 6, 7, 18]. However, these studies did not distinguish between CP and SP. Furthermore, previous studies on underlying diseases that examined only hospitalized patients were subject to potential selection bias because the worsening of underlying diseases could have caused hospitalization. As the majority of patients with influenza are treated in an outpatient setting, a large-scale study on both inpatients and outpatients is needed to establish evidence of the risk of pneumonia following influenza.

Knowledge of the different risk factors associated with CP and SP helps clinicians to maintain vigilance after diagnosis of influenza according to individual risks. Therefore, this study was conducted to identify the incidence rates of CP and SP following seasonal influenza and factors associated with their development using a large-scale health insurance claims database in Japan.

METHODS

Data Source

This study analyzed data from the claims database of JMDC, Inc. (Tokyo, Japan). The JMDC Claims Database, one of the largest public health care data sets in Japan, includes annual health check-up records, health insurance claims data, and ledger information [19, 20]. The database covers employees of medium- to large-scale companies and their dependents aged <75 years who subscribe to health insurance associations contracted by JMDC since 2005 [21]. The cumulative population in this database was ~13 million as of September 2021. This database contains demographic data such as year and month of birth, sex, and medical and pharmacy claims as follows: names and dates of medical practice; diagnosis based on International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), codes and diagnosis dates; drug names based on World Health Organization Anatomical Therapeutic Chemical codes, dosages, and prescription dates; and claim types, such as inpatient and outpatient [22].

Study Design and Population

This retrospective cohort study enrolled all patients who developed influenza at least once during 2 consecutive epidemic seasons from 2017 to 2019. The period between November 1, 2017, and April 30, 2018, was defined as the 2017/2018 season, and the period between November 1, 2018, and April 30, 2019, was defined as the 2018/2019 season.

In the main analysis, we defined patients as having influenza if they fulfilled the following criteria on the same date, which was designated as an index date: (1) examined with a rapid influenza diagnostic test (RIDT) that detects the influenza virus nucleoprotein antigen and (2) assigned ICD-10 codes of influenza as shown in Supplementary Table 1. If a patient had ≥2 diagnoses of influenza >14 days apart from each other, we counted the influenza occurrence in the same season. The last episode of influenza was analyzed when the patient had a repetitive case of influenza within the same epidemic season. To identify the underlying diseases, only patients with data registered >6 months before the index date were included. To assess the appropriateness of the definition of influenza in this study, we compared the number of total cases per week with the number of influenza cases newly diagnosed per week per sentinel site reported by the National Institute of Infectious Diseases for each epidemic season [23].

Patient Consent

As this study used anonymized claims data, the requirement for informed consent for enrollment was waived. This study was approved by the Institutional Review Board of the Graduate School of Medicine at the University of Tokyo (No. 10862-(3)).

Definition of Influenza-Related Bacterial Pneumonia

We defined patients as having bacterial pneumonia if they fulfilled the following criteria: (1) examined with x-ray and/or computed tomography, (2) assigned ICD-10 codes of bacterial pneumonia as shown in Supplementary Table 1 within 2 days of (1), and (3) started systemic antibiotics with WHO-ATC code J01 within 2 days of (1). We excluded cases with antibiotic prescriptions for >14 days at the time of pneumonia diagnosis because they were considered to have chronic infectious diseases (eg, pulmonary mycobacterial infection). CP was defined as bacterial pneumonia diagnosed between 3 days before and 6 days after the index date, whereas SP was defined as bacterial pneumonia diagnosed between 7 and 30 days after the index date [24]. Bacterial pneumonia diagnosed between 30 and 4 days before the index date was defined as pre-influenza pneumonia and served as a reference.

Study Variables

We categorized the patients into 4 groups: 0–6, 7–18, 19–64, and 65–74 years. The underlying diseases and medications used are listed in Supplementary Table 1. Chronic bronchitis/emphysema, cardiovascular disease, cerebrovascular disease, neurological disease, liver disease, renal disease, diabetes mellitus, malignant tumor, collagen vascular disease, and immunodeficiency disorder were identified according to ICD-10 codes. Patients with asthma were defined as those diagnosed with asthma and prescribed drugs for obstructive airway diseases more than once within the last 180 days before the index date. Patients with a diagnosis record of immunodeficiency disorders (Supplementary Table 1), those receiving chemotherapy, and those using immunosuppressants were defined as patients with immunosuppression. Patients undergoing chemotherapy had anticancer drugs prescribed more than once within the last 180 days before the index date. Immunosuppressant users were those prescribed immunosuppressive drugs more than once within the last 180

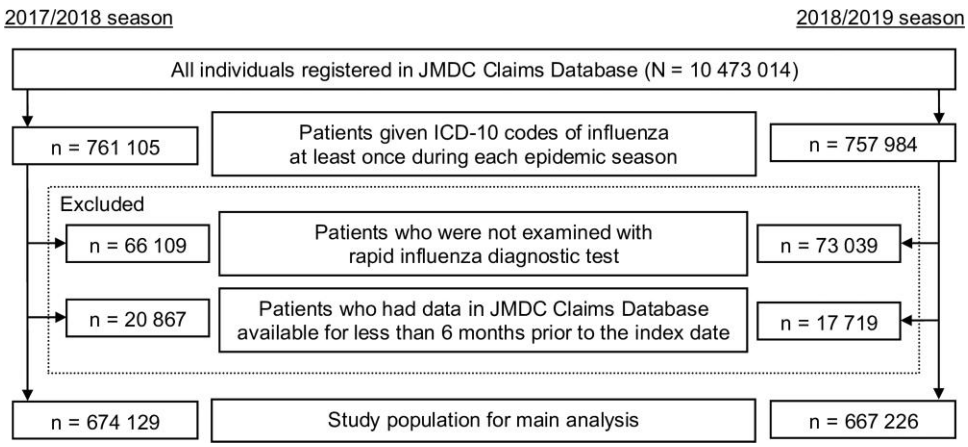

Figure 1. Flowchart of patients identified for the main analysis. Abbreviation: ICD-10, International Classification of Diseases and Related Health Problems, 10th Revision.

days before the index date and those prescribed systemic corticosteroids for a total of ≥30 days within the last 180 days before the index date.

Statistical Analyses

Categorical variables were presented as numbers with percentages and compared using the Pearson chi-square test. Continuous variables were presented as mean with standard deviation, and the Student *t* test and Mann-Whitney *U* test were used for comparison for normally distributed data and non–normally distributed data, respectively. To evaluate the factors associated with the development of CP and SP independently, multivariable analyses were performed using 2 logistic regression models. Patients diagnosed with CP were compared with the remaining patients to assess factors associated with its development. The patients diagnosed with SP were compared with others, except for those with CP, to assess factors associated with the development of SP, because it seemed rare that patients diagnosed with CP subsequently developed SP. We included repetitive cases of influenza in 1 season as an independent variable in the multivariable analyses to assess whether repetitive influenza increases the risk of bacterial pneumonia. Furthermore, anti-influenza drugs have been reported to suppress SP development, depending on the type of drug used [25]. Therefore, the types of anti-influenza drugs were also included as possible confounding factors in the multivariable regression model for SP. The variance inflation factor (VIF) for each independent variable was calculated to evaluate multicollinearity. All tests were 2-sided, and $P < .05$ was considered statistically significant. All statistical analyses were conducted using STATA, version 14.1 (StataCorp LP, College Station, TX, USA).

Sensitivity Analyses

Sensitivity analysis was performed to determine whether different definitions of influenza altered the results. In Japanese clinical practice, RIDTs are performed on ∼90% of patients with influenza-like illnesses, and anti-influenza drugs are prescribed to >90% of test-positive cases [26, 27]. Considering this Japanese management practice, patients who were not prescribed anti-influenza drugs may have had negative test results. Therefore, patients with "treated influenza" in sensitivity analysis were those prescribed anti-influenza drugs on the index date in addition to examination with RIDT and assigned the ICD-10 code for influenza. Using this definition, we identified the incidence and risk of CP and SP development in the aforementioned manner.

RESULTS

Study Population

Among the 10 473 014 individuals recorded in the JMDC Claims Database during the study period, 1 341 355 (674 129 in the 2017/2018 season and 667 226 in the 2018/2019 season) were eligible to be included in the main analysis (Figure 1). Supplementary Figure 1 illustrates the number of patients with influenza per week for each epidemic season, identified from the JMDC Claims Database and reported by the National Institute of Infectious Diseases, and shows the similarity between the 2 data sources in both seasons.

Patient Characteristics

Patient characteristics, stratified by age category and season, are presented in Table 1 and Supplementary Table 2, respectively. The mean age (SD) of all eligible patients was 26.6 (18.6) years, and the age category with the highest patient frequency was 19–64 years. The prevalence of each underlying disease was similar in both seasons; however, it was significantly different among age categories. Asthma was the most prevalent in the 0–6 years category, whereas all other diseases were common in patients aged 65–74 years. Influenza B was predominant in the 2017/2018 season, and influenza A was predominant in the 2018/2019 season. More than 90% of patients with influenza in all

Table 1. Baseline Characteristics of Patients

		Age Category			
	Total	0–6 y	7–18 y	19–64 y	65–74 y
No. of patients	1 341 355	185 560	426 799	712 217	16 779
Age, mean ± SD, y	26.6 ± 18.6	4.4 ± 1.5	11.5 ± 3.2	40.5 ± 11.9	67.9 ± 2.7
Male	730 367 (54.5%)	97 268 (52.4%)	227 846 (53.4%)	396 316 (55.7%)	8937 (53.3%)
Underlying disease					
Asthma	188 185 (14.0%)	82 111 (44.3%)	64 733 (15.2%)	39 896 (5.6%)	1445 (8.6%)
Chronic bronchitis/emphysema	33 756 (2.5%)	3337 (1.8%)	7162 (1.7%)	21 698 (3.1%)	1559 (9.3%)
Cardiovascular disease	87 470 (6.5%)	5020 (2.7%)	11 082 (2.6%)	65 716 (9.2%)	5652 (33.7%)
Cerebrovascular disease	29 463 (2.2%)	234 (0.13%)	1023 (0.24%)	25 114 (3.5%)	3092 (18.4%)
Neurological disease	141 511 (10.6%)	2846 (1.5%)	18 162 (4.3%)	115 756 (16.3%)	4747 (28.3%)
Liver disease	24 265 (1.8%)	357 (0.19%)	1250 (0.29%)	21 376 (3.0%)	1282 (7.6%)
Renal disease	24 880 (1.9%)	2852 (1.5%)	7123 (1.7%)	13 969 (2.0%)	936 (5.6%)
Diabetes mellitus	65 384 (4.9%)	161 (0.09%)	1770 (0.41%)	58 085 (8.2%)	5368 (32.0%)
Malignant tumor	20 927 (1.6%)	216 (0.12%)	902 (0.21%)	17 665 (2.5%)	2144 (12.8%)
Collagen vascular disease	22 079 (1.7%)	2953 (1.6%)	4991 (1.2%)	13 305 (1.9%)	830 (5.0%)
Immunosuppression	16 063 (1.2%)	1268 (0.68%)	2951 (0.69%)	11 199 (1.6%)	645 (3.8%)
Inpatient at influenza diagnosis	1477 (0.11%)	567 (0.31%)	268 (0.06%)	545 (0.08%)	97 (0.58%)
No. of influenza occurrences per season					
1	1 312 005 (97.8%)	176 014 (94.9%)	413 726 (96.9%)	705 589 (99.1%)	16 676 (99.4%)
2	28 914 (2.2%)	9326 (5.0%)	12 910 (3.0%)	6577 (0.92%)	101 (0.60%)
≥3	436 (0.03%)	220 (0.12%)	163 (0.04%)	51 (0.01%)	2 (0.01%)
Types of influenza virus					
A	622 679 (46.4%)	85 450 (46.1%)	171 212 (40.1%)	358 012 (50.3%)	8005 (47.7%)
B	293 378 (21.9%)	41 382 (22.3%)	118 944 (27.9%)	129 526 (18.2%)	3526 (21.0%)
Unknown	425 298 (31.7%)	58 728 (31.7%)	136 643 (32.0%)	224 679 (31.6%)	5248 (31.3%)
Anti-influenza drug					
Baloxavir	276 595 (20.6%)	12 429 (6.7%)	82 217 (19.3%)	178 094 (25.0%)	3855 (23.0%)
Oseltamivir	369 583 (27.6%)	139 252 (75.0%)	59 624 (14.0%)	165 742 (23.3%)	4965 (29.6%)
Laninamivir	476 355 (35.5%)	12 571 (6.8%)	180 809 (42.4%)	277 154 (38.9%)	5821 (34.7%)
Zanamivir	122 851 (9.2%)	5825 (3.1%)	80 537 (18.9%)	35 907 (5.0%)	582 (3.5%)
Peramivir	21 777 (1.6%)	1532 (0.83%)	3955 (0.93%)	15 627 (2.2%)	663 (4.0%)
No prescription	74 194 (5.5%)	13 951 (7.5%)	19 657 (4.6%)	39 693 (5.6%)	893 (5.3%)

age categories were prescribed anti-influenza drugs. The most frequently prescribed anti-influenza drug in the 2017/2018 season was laninamivir, which was superseded by baloxavir in the 2018/2019 season.

Incidence of Influenza-Related Bacterial Pneumonia

The number of patients with bacterial pneumonia diagnosed between 30 days before and after the index date is shown in Figure 2. Among the 1 341 355 patients with influenza, 2901 (0.22%) and 1262 (0.09%) developed CP and SP, respectively. The overall incidence of influenza-related bacterial pneumonia, including CP and SP, was 0.44% (816/185 560) in the age group 0–6 years, 0.19% (831/426 799) in 7–18 years, 0.33% (2319/712 217) in 19–64 years, and 1.17% (197/16 779) in those aged 65–74 years ($P < .001$). CP and SP occurred at an average (SD) of 2.2 (2.2) days and 15.3 (7.0) days after the diagnosis of influenza, respectively. Among the 643 patients who were diagnosed with pre-influenza pneumonia, 12 developed CP and 10 SP.

The incidences of CP and SP in inpatients with influenza were significantly higher ($P < .001$) than those in outpatients (10.8% [159/1477] vs 0.20% [2742/1 339 878], and 0.45% [6/1319] vs 0.09% [1256/1 337 148]) (Tables 2 and 3). The incidences of CP and SP in patients with type A influenza were almost equivalent to those in patients with type B influenza (0.18% [1138/622 679] vs 0.20% [586/293 378], and 0.10% [642/621 545] vs 0.07% [210/292 795], respectively) (Tables 2 and 3). Regarding anti-influenza drugs, the incidences of SP in patients prescribed baloxavir, oseltamivir, laninamivir, zanamivir, peramivir, and no drugs were 0.09% (246/276 213), 0.12% (449/368 873), 0.07% (348/475 580), 0.06% (74/122 712), 0.17% (36/21 542), and 0.15% (109/73 547), respectively (Table 3).

Factors Associated With CP Development

Table 2 shows the results of the univariable and multivariable analyses of factors associated with CP development. In the univariable analysis, all variables except sex were associated with CP development. The multivariable analysis showed that patients aged 0–6 and 65–74 years had a higher risk of developing CP than those aged 19–64 years, while patients aged 7–18 years had a lower risk. Repetitive cases of influenza increased the risk

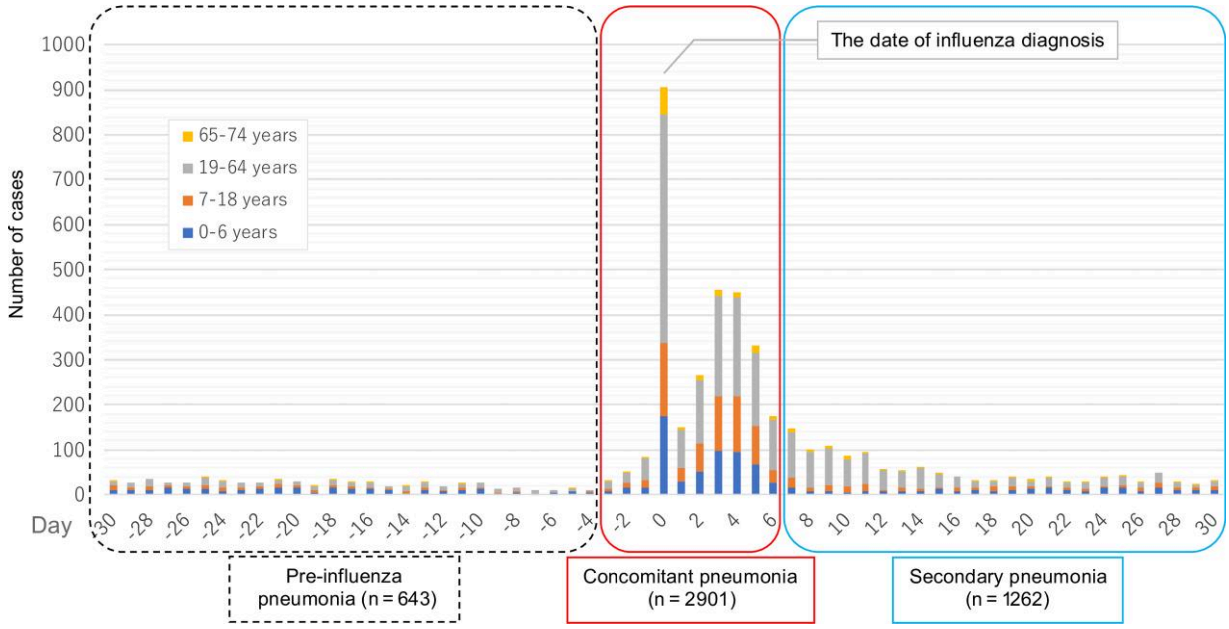

Figure 2. The number of patients with bacterial pneumonia diagnosed between 30 days before and 30 days after the date of influenza diagnosis, which was designated as the index date (day 0). Pre-influenza pneumonia, concomitant pneumonia, and secondary pneumonia were defined as bacterial pneumonia diagnosed between 30 and 4 days before the index date, between 3 days before and 6 days after the index date, and between 7 and 30 days after the index date, respectively.

of CP development (3.7% vs 2.2%; $P < .001$). Among the underlying diseases, asthma, chronic bronchitis/emphysema, cardiovascular disease, cerebrovascular disease, neurological disease, liver disease, renal disease, diabetes, malignant tumor, and immunosuppression were significantly associated with CP development. In particular, the adjusted odds ratio reached ∼2 for 4 variables: age 65–74 years, asthma, chronic bronchitis/emphysema, and immunosuppression. The VIF was close to 1, and no correlation between the variables was suggested.

Factors Associated With SP Development

Table 3 shows the results of the univariable and multivariable analyses for factors associated with SP development. In the univariable analysis, all variables were associated with SP development. The multivariable analysis showed that patients aged 65–74 years had a higher risk for developing SP than those aged 19–64 years, while those aged 0–6 and 7–18 years had a lower risk. Male sex and underlying diseases, including asthma, chronic bronchitis/emphysema, cardiovascular disease, renal disease, malignant tumor, and immunosuppression, were significantly associated with SP after adjustment for anti-influenza drugs prescribed at the time of influenza diagnosis. In particular, the adjusted odds ratio exceeded 2 for 3 variables: age 65–74 years, asthma, and chronic bronchitis/emphysema. No multicollinearity was suggested in the VIF.

Sensitivity Analyses

A total of 1 266 240 individuals were included in the sensitivity analysis, where we defined "treated influenza" as anti-influenza drugs being prescribed on the index date. Of these patients, 2201 (0.17%) and 1162 (0.09%) developed CP and SP, respectively. Factors associated with the development of CP and SP among patients with "treated influenza" are shown in Supplementary Tables 3 and 4, respectively. Old age and several underlying diseases were identified as risks of CP and SP development, which was consistent with the main analysis findings.

DISCUSSION

In this study, we clarified the incidence of CP and SP related to seasonal influenza in patients aged <75 years and evaluated the factors associated with their development using a health insurance claims database. The incidences of CP and SP were 0.22% and 0.09%, respectively, and were highest in older adults aged 65–74 years and lowest in youth aged 7–18 years. Old age, asthma, chronic bronchitis/emphysema, cardiovascular disease, renal disease, malignant tumor, and immunosuppression were risk factors associated with the development of both types of pneumonia. Cerebrovascular disease, neurological disease, liver disease, and diabetes were identified as risk factors specific to CP. These findings remained robust in the sensitivity analysis. To our knowledge, this is the first large-scale study to evaluate the incidence and risk factors of CP and SP separately.

Previous research on seasonal influenza-related bacterial pneumonia included only hospitalized patients, whereas we clarified the incidence by analyzing all outpatients and inpatients diagnosed with influenza. According to several reports using population-based surveillance data collected from the Centers for Disease

Table 2. Factors Associated With the Development of Concomitant Pneumonia

	Concomitant Pneumonia		Univariable			Multivariable	
	(+)	(–)	OR (95% CI)	*P* Value	VIF	aOR (95% CI)	*P* Value
No. of patients	2901 (0.22%)	1 338 454 (99.8%)	…		…	…	…
Age category, y	…	…	…	<.001	…	…	…
0–6	580 (20.0%)	184 980 (13.8%)	…		1.33	1.17 (1.05–1.31)	.005
7–18	646 (22.3%)	426 153 (31.8%)	…		1.21	0.746 (0.676–0.823)	<.001
19–64	1539 (53.1%)	710 678 (53.1%)	…		ref.	ref.	ref.
65–74	136 (4.7%)	16 643 (1.2%)	…		1.05	2.16 (1.78–2.60)	<.001
Male	1603 (55.3%)	728 764 (54.5%)	1.03 (0.960–1.11)	.382	1.01	1.03 (0.960–1.11)	.386
Underlying disease							
Asthma	843 (29.1%)	187 342 (14.0%)	2.52 (2.32–2.73)	<.001	1.17	2.36 (2.16–2.59)	<.001
Chronic bronchitis/emphysema	229 (7.9%)	33 527 (2.5%)	3.34 (2.91–3.82)	<.001	1.02	1.98 (1.71–2.28)	<.001
Cardiovascular disease	402 (13.9%)	87 068 (6.5%)	2.31 (2.08–2.57)	<.001	1.13	1.41 (1.25–1.60)	<.001
Cerebrovascular disease	169 (5.8%)	29 294 (2.2%)	2.77 (2.37–3.23)	<.001	1.09	1.48 (1.25–1.76)	<.001
Neurological disease	501 (17.3%)	141 010 (10.5%)	1.77 (1.61–1.95)	<.001	1.09	1.33 (1.20–1.48)	<.001
Liver disease	128 (4.4%)	24 137 (1.8%)	2.51 (2.10–3.00)	<.001	1.05	1.41 (1.16–1.71)	.001
Renal disease	131 (4.5%)	24 749 (1.9%)	2.51 (2.11–2.99)	<.001	1.03	1.55 (1.29–1.86)	<.001
Diabetes mellitus	319 (11.0%)	65 065 (4.9%)	2.42 (2.15–2.72)	<.001	1.16	1.38 (1.19–1.58)	<.001
Malignant tumor	133 (4.6%)	20 794 (1.6%)	3.05 (2.56–3.63)	<.001	1.06	1.54 (1.27–1.86)	<.001
Collagen vascular disease	88 (3.0%)	21 991 (1.6%)	1.87 (1.51–2.32)	<.001	1.04	0.982 (0.787–1.23)	.874
Immunosuppression	125 (4.3%)	15 938 (1.2%)	3.74 (3.12–4.47)	<.001	1.07	1.95 (1.60–2.37)	<.001
Inpatient at influenza diagnosis	159 (5.5%)	1318 (0.10%)	58.8 (49.7–69.6)	<.001	…	…	…
Repetitive case of influenza	107 (3.7%)	29 243 (2.2%)	1.72 (1.41–2.08)	<.001	1.01	1.46 (1.20–1.78)	<.001
Types of influenza virus	…	…	…	<.001	…	…	…
A	1138 (39.2%)	621 541 (46.4%)	…		ref.	ref.	ref.
B	586 (20.2%)	292 792 (21.9%)	…		1.17	1.12 (1.01–1.24)	.025
Unknown	1177 (40.6%)	424 121 (31.7%)	…		1.15	1.51 (1.39–1.64)	<.001
Anti-influenza drug	…	…	…	<.001	…	…	…
Baloxavir	383 (13.2%)	276 212 (20.6%)	…		…	…	…
Oseltamivir	713 (24.6%)	368 870 (27.6%)	…		…	…	…
Laninamivir	780 (26.9%)	475 575 (35.5%)	…		…	…	…
Zanamivir	139 (4.8%)	122 712 (9.2%)	…		…	…	…
Peramivir	237 (8.2%)	21 540 (1.6%)	…		…	…	…
No prescription	649 (22.4%)	73 545 (5.5%)	…		…	…	…

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; VIF, variance inflation factor.

Control and Prevention's Emerging Infectious Program Network, the incidence of pneumonia in hospitalized patients with laboratory-confirmed seasonal influenza was 29.2% (1392/4765)−35.4% (1868/5270) for those aged ≥18 years [2, 6] and 23.1% (1027/4439)−26.7% (1072/4015) for those aged ≤18 years [3, 7]. In contrast, few studies have been conducted in outpatients diagnosed with influenza. A recent study using a large-scale insurance claims database in Japan reported that the incidence rate of pneumonia within 28 days of influenza diagnosis was 0.53% (55/10 449), 1.62% (117/7221), 5.28% (221/4185), and 9.04% (344/3804) in the age groups 18–64, 65–74, 75–84, and ≥85 years, respectively [28], higher than the rates of those with influenza-related bacterial pneumonia, including CP and SP, in the present study. This discrepancy might be partially explained by differences in the definition of pneumonia. The diagnosis of pneumonia in most previous studies, including the aforementioned study, was based solely on ICD-10 codes without radiological examination, which potentially misclassified the disease [29]. In contrast, our definition of bacterial pneumonia based on ICD-10 codes combined with claim records of imaging and prescription may have increased the specificity of the diagnosis.

We analyzed cases of bacterial pneumonia diagnosed within 30 days before and after the diagnosis of influenza and found that bacterial pneumonia occurred more frequently after than before the diagnosis of influenza. Moreover, the number of cases per day occurring within 6 days after influenza diagnosis was ~5 times higher than that occurring between 7 and 30 days after diagnosis. In a previous study, the timing for the occurrence of bacterial pneumonia following influenza infection demonstrated a bimodal peak; the early-onset period of 0–6 days after influenza was more frequent than the late-onset period of 14–20 days (matched odds ratio, 8.3 vs 2.5) [24]. These findings indicate that the risk of developing bacterial pneumonia may increase in the early period after influenza infection.

In the present study, age 65–74 years, asthma, chronic bronchitis/emphysema, and immunosuppression were associated

Table 3. Factors Associated With the Development of Secondary Pneumonia

	Secondary Pneumonia		Univariable			Multivariable	
	(+)	(–)	OR (95% CI)	*P* Value	VIF	aOR (95% CI)	*P* Value
No. of patients	1262 (0.09%)	1 337 205 (99.9%)	…		…	…	…
Age category, y	…	…	…	<.001	…	…	…
0–6	236 (18.7%)	184 745 (13.8%)	…		1.53	0.787 (0.658–0.941)	.009
7–18	185 (14.7%)	425 968 (31.9%)	…		1.26	0.420 (0.354–0.498)	<.001
19–64	780 (61.8%)	709 906 (53.1%)	…		ref.	ref.	ref.
65–74	61 (4.8%)	16 586 (1.2%)	…		1.05	2.33 (1.77–3.07)	<.001
Male	630 (49.9%)	728 140 (54.5%)	0.834 (0.747–0.931)	.001	1.01	0.837 (0.749–0.936)	.002
Underlying disease							
Asthma	317 (25.1%)	187 033 (14.0%)	2.06 (1.82–2.34)	<.001	1.17	2.07 (1.79–2.39)	<.001
Chronic bronchitis/emphysema	106 (8.4%)	33 424 (2.5%)	3.58 (2.93–4.37)	<.001	1.02	2.29 (1.85–2.82)	<.001
Cardiovascular disease	157 (12.4%)	86 916 (6.5%)	2.04 (1.73–2.42)	<.001	1.13	1.31 (1.09–1.58)	.004
Cerebrovascular disease	48 (3.8%)	29 247 (2.2%)	1.77 (1.33–2.36)	<.001	1.09	0.935 (0.687–1.27)	.669
Neurological disease	192 (15.2%)	140 821 (10.5%)	1.52 (1.31–1.78)	<.001	1.05	1.07 (0.906–1.26)	.430
Liver disease	45 (3.6%)	24 094 (1.8%)	2.02 (1.50–2.71)	<.001	1.05	1.16 (0.850–1.59)	.348
Renal disease	48 (3.8%)	24 702 (1.9%)	2.10 (1.57–2.80)	<.001	1.03	1.43 (1.06–1.94)	.020
Diabetes mellitus	118 (9.4%)	64 953 (4.9%)	2.02 (1.67–2.44)	<.001	1.16	1.12 (0.900–1.40)	.307
Malignant tumor	55 (4.4%)	20 740 (1.6%)	2.89 (2.21–3.79)	<.001	1.06	1.47 (1.10–1.96)	.009
Collagen vascular disease	46 (3.7%)	21 947 (1.6%)	2.27 (1.69–3.04)	<.001	1.04	1.31 (0.957–1.79)	.092
Immunosuppression	50 (4.0%)	15 889 (1.2%)	3.43 (2.58–4.55)	<.001	1.07	1.78 (1.32–2.42)	<.001
Inpatient at influenza diagnosis	6 (0.48%)	1313 (0.10%)	4.86 (2.18–10.9)	<.001	…	…	…
Repetitive case of influenza	38 (3.0%)	29 205 (2.2%)	1.39 (1.01–1.92)	.045	1.02	1.37 (0.985–1.90)	.061
Types of influenza virus	…	…	…	<.001	…	…	…
A	642 (50.9%)	620 903 (46.4%)	…		ref.	ref.	ref.
B	210 (16.6%)	292 585 (21.9%)	…		1.28	0.748 (0.636–0.880)	<.001
Unknown	410 (32.5%)	423 717 (31.7%)	…		1.21	0.902 (0.792–1.03)	.119
Anti-influenza drug	…	…	…	<.001	…	…	…
Baloxavir	246 (19.5%)	275 967 (20.6%)	…		4.01	0.591 (0.467–0.749)	<.001
Oseltamivir	449 (35.6%)	368 424 (27.6%)	…		4.54	0.770 (0.620–0.957)	.018
Laninamivir	348 (27.6%)	475 232 (35.5%)	…		5.03	0.557 (0.447–0.695)	<.001
Zanamivir	74 (5.9%)	122 638 (9.2%)	…		2.54	0.587 (0.434–0.794)	.001
Peramivir	36 (2.9%)	21 506 (1.6%)	…		1.29	0.951 (0.648–1.40)	.798
No prescription	109 (8.6%)	73 438 (5.5%)	…		ref.	ref.	ref.

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; VIF, variance inflation factor.

with an increased risk of developing CP, with an adjusted odds ratio near 2. The incidence of community-acquired pneumonia is reported to be significantly higher in patients with these risks [30, 31]. Three main pathogeneses are associated with CP development: increased bacterial colonization in the lower respiratory tract due to impaired mucociliary clearance, enhanced bacterial adhesion to the airway epithelium, and impairment of the host's innate immunity against bacteria [9, 17, 32–34]. Direct damage to the airway epithelium by the influenza virus is most severe 6 days postinfection [32]. Considering that the incubation period for the influenza virus is ∼2 days, bacterial coinfection is more likely to occur within 1 week after the onset of influenza symptoms. Furthermore, in asthma and chronic bronchitis/emphysema, structural and functional changes in the airways due to chronic inflammation impair mucociliary clearance and local immunity [35–37]. Patients with chronic obstructive pulmonary disease have a high frequency of bacterial colonization, with bacteria such as *Haemophilus influenzae*, in the lower respiratory tract and impaired phagocytosis by alveolar macrophages [38, 39], which further increases the risk of developing CP following influenza infection. These mechanisms underlie our finding that patients with asthma and chronic bronchitis/emphysema are at a high risk of CP. In addition, older adults and immunosuppressed individuals are more susceptible to CP due to decreased host immunity. Indeed, clinical research on the 2009 influenza pandemic reported that immunosuppression significantly increased the risk of mortality due to bacterial coinfection [40].

In the present study, age 65–74 years, asthma, and chronic bronchitis/emphysema were risk factors for developing SP, with an adjusted odds ratio >2. Clearance of bacteria by airway-resident alveolar macrophages is most significantly inhibited 7–8 days after influenza infection, followed by a gradual recovery ∼>2 weeks [32, 33]. Therefore, even after the disappearance of the influenza virus from the lower respiratory tract, the risk of SP may remain high up to 3–4 weeks postinfection.

The risk of developing SP and CP may be particularly high in older patients and those with asthma or chronic bronchitis/emphysema because of the impaired local immunity of the lower respiratory tract.

The findings of this study indicate that clinicians should maintain vigilance for patients with any of the following 7 factors associated with the development of CP and SP, not only within the first week after influenza infection but also for at least 1 month: age 65–74 years, asthma, chronic bronchitis/emphysema, immunosuppression (with immunodeficiency disorder, anticancer therapy, or immunosuppressive drugs), cardiovascular disease, renal disease, and malignancy. In contrast, patients with cerebrovascular, neurological, and liver diseases, as well as diabetes, require caution for CP, especially early after the onset of influenza. The effectiveness of active interventions, such as imaging and prophylactic prescription of antimicrobial agents, for these high-risk patients requires further investigation.

This study has several limitations that should be acknowledged. First, the JMDC Claims Database includes employees of medium- to large-scale companies and their employees aged <75 years. This is because all older adults aged ≥75 years are covered by Late Elders' Health Insurance in Japan [21]. Furthermore, most individuals aged ≥65 years were excluded from the database, as retired individuals generally withdraw from the employment-based health insurance system. Additionally, covered workers were likely to be socially advantaged, which may result in better health [41]. The applicability of our findings to older adults and those insured under other types of insurance needs to be verified using another data set. Second, the database does not include information on examination results [22]. Therefore, some of the cases defined as influenza or bacterial pneumonia in this study may have been overdiagnosed (eg, considered the occurrence of disease despite negative test results). Third, the database did not contain information on individuals' vaccination status or the severity of underlying diseases. Vaccination status may have affected the incidence of influenza-related bacterial pneumonia, as both influenza and pneumococcal vaccination reduce the risk of influenza complications (including pneumonia) [42–44]. Finally, we cannot rule out the possibility that primary influenza pneumonia was included in CP in this study because it is difficult to clinically distinguish between these 2 types of pneumonia [17].

In conclusion, our study, using a large-scale health insurance claims database, clarified the incidences of CP and SP related to seasonal influenza in patients aged <75 years and factors associated with their development. The findings of this study will not only contribute to knowledge on the epidemiology of influenza but also help clinicians in primary care settings determine when to be alert for the development of bacterial pneumonia after influenza infection, depending on a patient's background.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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