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Risk Factors for Pneumonia and Death in Adult Patients With Seasonal Influenza and Establishment of Prediction Scores: A Population-Based Study

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Background. Seasonal influenza remains a global health problem; however, there are limited data on the specific relative risks for pneumonia and death among outpatients considered to be at high risk for influenza complications. This population-based study aimed to develop prediction models for determining the risk of influenza-related pneumonia and death.

Methods. We included patients diagnosed with laboratory-confirmed influenza between 2016 and 2017 (main cohort, n = 25 659), those diagnosed between 2015 and 2016 (validation cohort 1, n = 16 727), and those diagnosed between 2017 and 2018 (validation cohort 2, n = 34 219). Prediction scores were developed based on the incidence and independent predictors of pneumonia and death identified using multivariate analyses, and patients were categorized into low-, medium-, and high-risk groups based on total scores.

Results. In the main cohort, age, gender, and certain comorbidities (dementia, congestive heart failure, diabetes, and others) were independent predictors of pneumonia and death. The 28-day pneumonia incidence was 0.5%, 4.1%, and 10.8% in the low-, medium-, and high-risk groups, respectively (c-index, 0.75); the 28-day mortality was 0.05%, 0.7%, and 3.3% in the low-, medium-, and high-risk groups, respectively (c-index, 0.85). In validation cohort 1, c-indices for the models for pneumonia and death were 0.75 and 0.87, respectively. In validation cohort 2, c-indices for the models were 0.74 and 0.87, respectively.

Conclusions. We successfully developed and validated simple-to-use risk prediction models, which would promptly provide useful information for treatment decisions in primary care settings.

Keywords. seasonal influenza; prediction model; mortality rate; pneumonia; insurance claims data.

Seasonal influenza has been identified as an infectious disease that is prevalent, especially during winter, and is caused by the influenza A and B viruses [1, 2]. Up to 20% of the world's population contracts influenza each year, and pandemic can occur when novel strains emerge [1, 3, 4]. Most patients with influenza recover within a week without specific treatment, but some develop severe complications, leading to hospitalization or even death. Although estimated annual influenza-related mortality among patients infected is <0.1%, more than 500 000–600 000 people reportedly die worldwide from influenza or influenza-related complications annually due to the large number of influenza-infected patients [5–7]. Therefore, influenza remains a serious global health problem.

Pneumonia is a common complication of influenza, and it can be primary influenza pneumonia, mixed pneumonia due to virus and bacteria, or secondary bacterial pneumonia [8, 9]. Primary influenza pneumonia is caused by the influenza virus, but bacterial infections may sometimes overlap. Secondary bacterial pneumonia can develop within a few days to a week of influenza onset, and occasionally later [8, 9]. Despite distinct pathologies, these types of pneumonia are clinically similar and can substantially contribute to mortality [9–12]. Thus, early identification and treatment of individuals at high risk of severe influenza, and especially pneumonia, may help in reducing complication incidence and mortality, thereby improving disease burden. Several studies have described risk factors for pneumonia development and death among influenza patients [12–17]; however, these studies only analyzed data from patients hospitalized for influenza. As most patients with influenza are outpatients, large-scale studies that use data from all patients diagnosed with influenza are needed to establish evidence for such a serious clinical event in a general population.

Therefore, using the Shizuoka Kokuho Database (SKDB), a large-scale insurance claims database of the Shizuoka prefecture in Japan, this population-based study examined the incidence of pneumonia and mortality to identify their predictive factors in adult patients with laboratory-confirmed influenza.

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Furthermore, based on these identified predictors, we attempted to develop a simple-to-use prediction score for determining the risk of pneumonia and death.

METHODS

Data Source and Patients

This population-based retrospective study utilized the SKDB, an insurance claims database in Shizuoka prefecture, Japan, which includes data from the National Health Insurance and the Latter-Stage Elderly Medical Care System for prefectural residents in Shizuoka, Japan. The database contains information relating to age; gender; diagnosis based on *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10); prescribed drugs and their date of administration; and survival outcomes. The SKDB has a subscriber's list for insurances. The multiple identifiers caused by a change of insurance system were unified into 1 for each individual based on the match of zip code, gender, and birthday. Therefore, in the SKDB, 1 individual has only 1 identifier, and there is no bias due to duplication. Furthermore, the SKDB provides data on the causes of insurance withdrawal, such as changes in the insurance system, changes in address, death, and withdrawal dates. Therefore, all deaths were identified, and all death dates were included. This study cohort includes both subscribers living at home independently and those residing in facilities such as elderly nursing homes or assisted living facilities, but this database does not have accurate information on whether the subscribers reside in those facilities.

The Shizuoka prefecture is located in central Japan, has a population of ~3.7 million, and is characterized by standard climate, demographics, and economy in Japan. The SKDB covers ~21%, ~73%, and ~96% of residents aged 18–64 years, 65–74 years, and ≥75 years, respectively, which corresponds to >1.3 million residents and coverage of ~35% in 2016. We extracted data on adult patients aged ≥18 years who had been diagnosed with influenza (ICD-10 codes J10, J11) between September 2016 and August 2017 for the main cohort, between September 2015 and August 2016 for validation cohort 1, and between September 2017 and August 2018 for validation cohort 2; the latter 2 cohorts were used for evaluating prediction scores. Only laboratory-confirmed cases of influenza were included, and these were ascertained as influenza A or B by a rapid antigen detection test; the test has moderate–high sensitivity (59%–93%) and high specificity (98%–100%) [1, 18].

Patient Consent Statement

This study conformed to the tenets of the Declaration of Helsinki. The Ethics Committee of the Shizuoka General Hospital approved this study (approval number: SGHIRB#20190084) and waived the need for patient approval or informed consent due to its retrospective nature.

Outcome and Variables

We defined influenza-related pneumonia or influenza-related death as pneumonia or death within 28 days of influenza diagnosis. In patients who were not followed up for more than 28 days after an influenza diagnosis, the date of the last visit was defined as the date of censoring. Data pertaining to the following variables were extracted from the SKDB database: age, gender, date of influenza diagnosis, influenza type (A or B), anti-influenza drug prescribed at the time of influenza diagnosis, date of pneumonia diagnosis (ICD-10 codes J 110, 13–16, and 18), and date of death, if applicable. We also extracted data regarding comorbidities listed in the Charlson Comorbidity Index (Supplementary Table 1), which has been widely used for evaluating risk adjustment in outcome studies that use health insurance claims data [19–22].

Statistical Analysis

Continuous and categorical variables were expressed as mean ± SD or median (range) and number (%), respectively. The Student *t* test for continuous variables and the chi-square test for categorical variables were used for between-group comparisons. Meanwhile, Poisson regression analysis was used to identify risk factors for pneumonia occurrence within 28 days, and risk ratios, 95% CIs, and *P* values based on the Wald test were also calculated. To identify prognostic factors of death within 28 days, Cox regression analysis, with and without time-dependent covariates, was used; thereafter, hazard ratios, 95% CIs, and *P* values based on the Wald test were calculated. Age, gender, all variables considered clinically significant, specifically risk factors already reported in hospital-based studies or small population-based studies [12–17], and all variables that were statistically significant in univariate analyses were included in multivariable analyses [23]. However, 1 of the 2 variables with a high correlation (the absolute value of Spearman's correlation coefficient >0.4) was not used in the multivariate model because of multicollinearity, and the variable used was selected on the basis of clinical importance.

To develop prediction scores for pneumonia and death within 28 days, risk ratio/hazard ratio values were converted to logarithms, doubled, and rounded to the nearest integer [24]. Their discrimination performance was evaluated using the c-index. We assessed model calibration by comparing observed vs predicted risk at each level of the scores and performed the Hosmer-Lemeshow goodness-of-fit test by 10th percentiles. The development of these prediction models and prediction scores conformed to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [25].

There were no missing data for any of the variables used in this study. $P < .05$ was considered statistically significant. Statistical analyses were performed using R (version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria) and JMP (version 13.2.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Figure 1 provides the flow diagram of the process used for selecting the cases for the main cohort. Briefly, of the 41 069 adult patients diagnosed with influenza, 15 410 with non-laboratory-confirmed influenza were excluded; consequently, 25 659 cases with laboratory-confirmed influenza were included in the main cohort. No difference was determined in the baseline characteristics between the laboratory-confirmed influenza and non-laboratory-confirmed influenza groups (Supplementary Table 2). Among the confirmed cases, 207 (0.8%) were censored within 28 days of influenza diagnosis, with a median time period (range) of 12 (0–27) days.

The characteristics of patients with laboratory-confirmed influenza in the main cohort are shown in Table 1. Most patients (94.7%) were diagnosed with influenza A, and all patients were treated with an anti-influenza drug, which was prescribed on the same date of influenza diagnosis.

Incidence of Pneumonia and Mortality Within 28 Days After Influenza Diagnosis

Within 28 days of the influenza diagnosis, pneumonia occurred in 737 (2.9%; 737/25 659) patients, while 162 (0.6%) died, and 28-day mortality was higher in patients with pneumonia than in those without pneumonia (5.7% vs 0.5%; $P < .001$). The number of patients with pneumonia and the time to diagnosis, along with the number of patients who died and the time from influenza diagnosis to death, are shown in Supplementary Figure 1, A and B, respectively. Supplementary Figure 2A shows the 28-day incidence of pneumonia by age group, which was 0.53% in 18–64-year-olds, 1.62% in 65–74-year-olds, 5.28% in 75–84-year-olds, and 9.04% in ≥85-year-olds. Supplementary Figure 2B shows the 28-day mortality by age group, which was 0.05% in 18–64-year-olds, 0.18% in 65–74-year-olds, 1.03% in 75–84-year-olds, and 2.66% in ≥85-year-olds.

Predictive Factors for Pneumonia or Death Within 28 Days

The correlation coefficients between the variables are shown in Supplementary Table 3. There were no pairs of variables with a Spearman's correlation coefficient absolute value >0.4. Multivariable analysis identified older age, male gender, dementia, congestive heart failure, chronic pulmonary disease, and diabetes mellitus as independent risk factors for incidence of pneumonia (Table 2), with a c-index of 0.80 (95% CI, 0.79–0.82).

Next, older age, dementia, congestive heart failure, liver disease, diabetes mellitus, and metastatic solid tumor were determined to be independent prognostic factors for death (Table 3), with a c-index of 0.89 (95% CI, 0.87–0.91).

In the Cox model, pneumonia diagnosis (as a time-dependent covariate) was associated with a higher 28-day mortality (adjusted hazard ratio, 3.94; 95% CI, 2.71–5.73) after adjustment for prognostic factors and anti-influenza drug prescribed at the time of influenza diagnosis.

Prediction Scores for Pneumonia Development and Death

The prediction score for pneumonia development was determined based on the risk ratios provided in Table 2 (Supplementary Table 4), and the total score for each individual ranged from 0 to 10 (Figure 2A). The model was graphically well calibrated, with close agreement between observed and predicted incidences of pneumonia at various score levels (Supplementary Figure 3A); however, the Hosmer-Lemeshow goodness-of-fit statistic was deemed significant ($\chi^2 = 16.7$; 8 degrees of freedom; $P = 0.033$), probably due to large sample size (n = 25 659).

Subsequently, based on total prediction scores, patients in the main cohort were categorized into 3 groups, low, medium, and

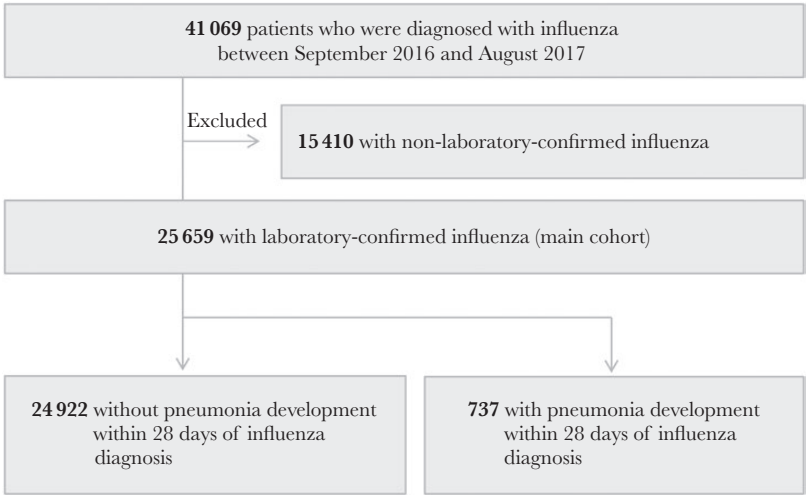


Figure 1. Flow diagram of the main cohort.

Table 1. Patient Characteristics

Variable	Category or Statistics	Total Influenza (n = 25 659)	Nonpneumonia (n = 24 922)	Pneumonia (n = 737)	*P* Value
Baseline characteristics					
Age, y		63.9 ± 20.0	63.3 ± 19.9	81.1 ± 12.1	<.001
Age, y	18–64	10 449 (40.7)	10 394 (41.7)	55 (7.5)	<.001
	65–74	7221 (28.1)	7104 (28.5)	117 (15.9)	
	75–84	4185 (16.3)	3964 (15.9)	221 (30.0)	
	85–	3804 (14.8)	3460 (13.9)	344 (46.7)	
Gender	Men	10 985 (42.8)	10 634 (42.7)	351 (47.6)	.008
Influenza type	A	24 309 (94.7)	23 604 (94.7)	705 (95.7)	.28
	B	1350 (5.3)	1318 (5.3)	32 (4.3)	
Anti-influenza drug	Oseltamivir	11 002 (42.9)	10 713 (43.0)	289 (39.2)	<.001
	Laninamivir	10 364 (40.4)	10 236 (41.1)	128 (17.4)	
	Zanamivir	1402 (5.5)	1390 (5.6)	12 (1.6)	
	Peramivir	2891 (11.3)	2583 (10.4)	308 (41.8)	
Baseline comorbidity					
Cerebrovascular disease	Presence	3838 (15.0)	3595 (14.4)	243 (33.0)	<.001
Any malignancy	Presence	2115 (8.2)	1992 (8.0)	123 (16.7)	<.001
Dementia	Presence	2124 (8.3)	1936 (7.8)	188 (25.5)	<.001
AIDS/HIV	Presence	5 (0.0)	5 (0.0)	0 (0.0)	>.99
Myocardial infarction	Presence	507 (2.0)	461 (1.8)	46 (6.2)	<.001
Renal disease	Presence	800 (3.1)	744 (3.0)	56 (7.6)	<.001
Congestive heart failure	Presence	3292 (12.8)	3022 (12.1)	270 (36.6)	<.001
Peripheral vascular disease	Presence	2134 (8.3)	2016 (8.1)	118 (16.0)	<.001
Chronic pulmonary disease	Presence	6971 (27.2)	6672 (26.8)	299 (40.6)	<.001
Rheumatic disease	Presence	658 (2.6)	628 (2.5)	30 (4.1)	.013
Peptic ulcer disease	Presence	3761 (14.7)	3587 (14.4)	174 (23.6)	<.001
Liver disease	Presence	3341 (13.0)	3219 (12.9)	122 (16.6)	<.001
Diabetes mellitus	Presence	1516 (5.9)	1415 (5.7)	101 (13.7)	<.001
Hemiplegia or paraplegia	Presence	253 (1.0)	238 (1.0)	15 (2.0)	<.001
Metastatic solid tumor	Presence	240 (0.9)	223 (0.9)	17 (2.3)	<.001

Data are presented as mean ± SD or No. (%).

Table 2. Poisson Regression Analysis for Pneumonia Development

		Univariate			Multivariable		
Variable (Reference)	Category	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Age (vs 18–64), y	65–74	3.08	2.23–4.24	<.001	2.71	1.96–3.75	<.001
	75–84	10.0	7.47–13.5	<.001	7.22	5.31–9.82	<.001
	85–	17.2	12.9–22.8	<.001	11.6	8.51–15.8	<.001
Men (vs women)	Men	1.21	1.05–1.40	.008	1.35	1.16–1.57	<.001
Influenza type (vs B)	A	1.22	0.86–1.74	.26			
Cerebrovascular disease (vs absence)	Presence	2.80	2.40–3.26	<.001	1.12	0.95–1.32	.19
Any malignancy (vs absence)	Presence	2.23	1.84–2.71	<.001	1.19	0.97–1.47	.10
Dementia (vs absence)	Presence	3.79	3.22–4.48	<.001	1.36	1.13–1.63	<.001
Myocardial infarction (vs absence)	Presence	3.30	2.45–4.45	<.001	1.31	0.96–1.79	.09
Renal disease (vs absence)	Presence	2.56	1.95–3.36	<.001	1.02	0.77–1.35	.90
Congestive heart failure (vs absence)	Presence	3.93	3.38–4.56	<.001	1.47	1.24–1.74	<.001
Peripheral vascular disease (vs absence)	Presence	2.10	1.73–2.56	<.001	1.03	0.84–1.26	.80
Chronic pulmonary disease (vs absence)	Presence	1.83	1.58–2.12	<.001	1.36	1.17–1.58	<.001
Rheumatic disease (vs absence)	Presence	1.61	1.12–2.32	.01	1.11	0.76–1.60	.59
Peptic ulcer disease (vs absence)	Presence	1.80	1.52–2.13	<.001	1.02	0.85–1.21	.84
Liver disease (vs absence)	Presence	1.33	1.09–1.61	.005	0.94	0.77–1.15	.56
Diabetes mellitus (vs absence)	Presence	2.53	2.05–3.12	<.001	1.56	1.25–1.94	<.001
Hemiplegia/paraplegia (vs absence)	Presence	2.09	1.25–3.48	.005	1.03	0.61–1.73	.91
Metastatic solid tumor (vs absence)	Presence	2.50	1.55–4.05	<.001	1.49	0.90–2.47	.12

Cases of AIDS/HIV infection were excluded from this analysis because there were too few patients in the cohort.

Abbreviation: RR, risk ratio.

Table 3. Cox Regression Hazards Analysis for Death

		Univariate			Multivariable		
Variable (Reference)	Category	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (vs 18–64), y	65–74	3.75	1.34–10.5	.012	2.83	1.00–7.98	.049
	75–84	21.5	8.51–54.2	<.001	10.7	4.14–27.6	<.001
	85–	55.8	22.7–137.0	<.001	22.7	8.88–58.1	<.001
Men (vs women)	Men	1.04	0.76–1.42	.79	1.21	0.87–1.68	.25
Influenza type (vs B)	A	3.75	1.34–10.5	.38			
Cerebrovascular disease (vs absence)	Presence	4.68	3.44–6.38	<.001	1.38	0.99–1.92	.057
Any malignancy (vs absence)	Presence	2.23	1.48–3.37	<.001	0.98	0.62–1.55	.93
Dementia (vs absence)	Presence	7.12	5.19–9.77	<.001	1.94	1.38–2.73	<.001
Myocardial infarction (vs absence)	Presence	5.49	3.27–9.19	<.001	1.70	0.99–2.92	.053
Renal disease (vs absence)	Presence	4.4	2.76–7.03	<.001	1.33	0.82–2.17	.25
Congestive heart failure (vs absence)	Presence	7.75	5.69–10.6	<.001	2.11	1.49–2.98	<.001
Peripheral vascular disease (vs absence)	Presence	3.05	2.1–4.43	<.001	1.19	0.81–1.77	.38
Chronic pulmonary disease (vs absence)	Presence	1.71	1.24–2.34	<.001	1.12	0.81–1.55	.48
Rheumatic disease (vs absence)	Presence	1.72	0.81–3.67	.16			
Peptic ulcer disease (vs absence)	Presence	1.98	1.39–2.82	<.001	0.92	0.64–1.33	.67
Liver disease (vs absence)	Presence	2.34	1.65–3.33	<.001	1.62	1.14–2.32	.008
Diabetes mellitus (vs absence)	Presence	3.2	2.12–4.83	<.001	1.69	1.10–2.60	.018
Hemiplegia/paraplegia (vs absence)	Presence	3.87	1.71–8.74	.001	1.46	0.64–3.37	.37
Metastatic solid tumor (vs absence)	Presence	4.84	2.27–10.3	<.001	3.13	1.37–7.16	<.001

Cases of AIDS/HIV infection were excluded from this analysis because there were too few patients in the cohort.

Abbreviation: HR, hazard ratio.

high risk, and these 3 groups were adjusted such that the estimated 28-day incidence of pneumonia was <1%, 1%–5%, and >5%, respectively. The 28-day incidence of pneumonia was 0.5% in the low-risk group (total score 0–2), 4.1% in the medium-risk group (total score 3–6), and 10.8% in the high-risk group (total score ≥7) (Figure 2B), and the c-index for this scoring was 0.75 (95% CI, 0.74–0.77).

The prediction score for death was determined based on the hazard ratios provided in Table 3 (Supplementary Table 5), and total scores for an individual ranged from 0 to 12 (Figure 2C). The model showed a good fit (Supplementary Figure 3B), and the Hosmer-Lemeshow goodness-of-fit statistic was found to be not significant ($\chi^2 = 7.65$; 8 degrees of freedom; $P = 0.47$).

Next, patients in the main cohort were categorized into 3 groups, low, medium, and high risk, based on their total scores, and the groups were then adjusted such that the estimated 28-day mortality was <0.1%, 0.1%–1%, and >1%, respectively. After adjustment, 28-day mortality was 0.05% in the low-risk group (total score 0–2), 0.7% in the medium-risk group (total score 3–6), and 3.3% in the high-risk group (total score ≥7, Figure 2D), with a c-index of 0.85 (95% CI, 0.83–0.88).

To summarize, for pneumonia, a score is given for each of the present variables (age, sex, and underlying disease); a total score of 3–6 indicates a moderate risk of pneumonia, and 7–10 indicates a high risk of pneumonia. For death, a score is given for each of the present variables (age and underlying disease); a total score of 3–6 indicates a moderate risk of death, and 7–12 indicates a high risk of death.

Validation of Prediction Score

Among the 28 175 patients diagnosed with influenza between September 2015 and August 2016 (Supplementary Figure 4A), 16 727 laboratory-confirmed cases of influenza were included in validation cohort 1 (Supplementary Table 6). Of these patients, 394 (2.4%) were diagnosed as having pneumonia, and 40 (0.2%) died within 28 days after influenza diagnosis. Among the 53 539 patients diagnosed with influenza between September 2017 and August 2018 (Supplementary Figure 4B), 34 219 patients with laboratory-confirmed influenza were included in validation cohort 2 (Supplementary Table 6). Of these, 884 (2.6%) patients were diagnosed as having pneumonia and 200 (0.6%) died within 28 days after influenza diagnosis.

The 28-day incidence of pneumonia in validations cohorts 1 and 2, respectively, was 0.7% and 0.6% in the low-risk group, 4.2% and 3.5% in the medium-risk group, and 13.4 % and 9.8% in the high-risk group, with c-indices of 0.75 (95% CI, 0.73–0.78) and 0.74 (95% CI, 0.73–0.76) (Supplementary Figure 5A). Next, 28-day mortality in validations cohorts 1 and 2, respectively, was 0.03% and 0.05% in the low-risk group, 0.4% and 0.7% in the medium-risk group, and 2.1% and 2.9% in the high-risk group, and the corresponding c-indices were 0.87 (95% CI, 0.81–0.92) and 0.87 (95% CI, 0.85–0.89) (Supplementary Figure 5B).

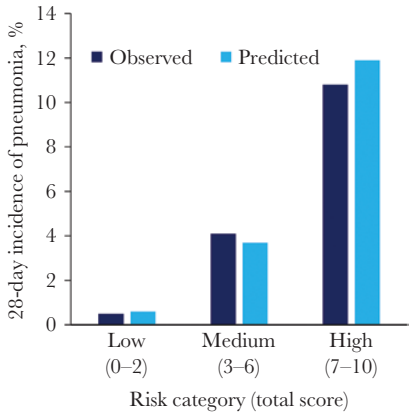
DISCUSSION

To the best of our knowledge, this is the first large-scale, population-based study that has used insurance claims data to

A

Category	Score
Age	
18–64	0
65–74	2
75–84	4
≧85	5
Man	1
Dementia	1
Congestive heart failure	1
Chronic pulmonary disease	1
Diabetes mellitus	1
Total score	0–10

B



C

Category	Score
Age	
18–64	0
65–74	2
75–84	5
≧85	6
Dementia	1
Congestive heart failure	1
Liver disease	1
Diabetes mellitus	1
Metastatic solid tumor	2
Total score	0–12

D

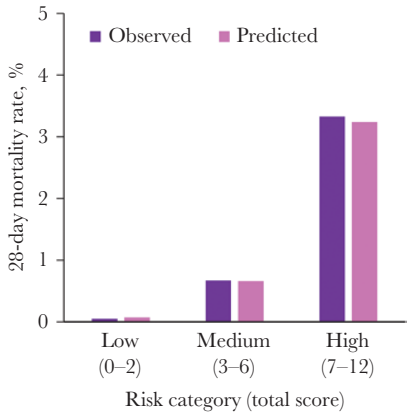


Figure 2. Prediction scores for pneumonia development and death. A, Table showing the relationship between risk factors of pneumonia development within 28 days after influenza diagnosis and patient scores. B, Incidence of pneumonia within 28 days after influenza diagnosis when categorized by risk category, which was determined by total score. C, Table showing the relationship between prognostic factors of death within 28 days after influenza diagnosis and patient scores. D, Mortality within 28 days after influenza diagnosis when categorized by risk category, which was determined by total score.

evaluate the incidence of pneumonia and mortality and to identify predictive factors of pneumonia and mortality in a general population of patients with laboratory-confirmed influenza. Furthermore, using these independent predictive factors, we were able to build a simple-to-use prediction score for influenza-related pneumonia and death that can be used for risk determination. In the main cohort, the incidence of pneumonia and mortality was higher in patients aged ≥65 years than in those aged <65 years; accordingly, multivariate analyses identified older age and certain comorbidities, such as dementia, congestive heart failure, and diabetes mellitus, as independent predictors of pneumonia and death. Developing influenza-related pneumonia also substantially increased 28-day mortality. The c-indices for our scores for pneumonia and death were 0.75 and 0.85 in the main cohort, respectively, 0.75 and 0.87 in validation cohort 1, respectively, and 0.74 and 0.87 in validation cohort 2, respectively.

We assigned scores to the identified risk factors according to the risk/hazard ratio, and patients were classified into low-, medium-, and high-risk groups according to the sum of the scores of their risk factors. For example, a 79-year-old man with dementia, chronic respiratory disease, and diabetes would be classified into the high-risk group for both pneumonia and death, as his total scores would be 8 for pneumonia and 7 for death (Figure 2). If our prediction models can identify high-risk patients, primary care physicians and public health centers can encourage such patients and their families/caregivers to be aggressively vaccinated and can routinely educate them on personal protective measures and the timing of medical visits during an influenza epidemic. These models could also help primary care physicians determine whether patients with influenza should be screened more aggressively for influenza-related complications including pneumonia, given antivirals/antimicrobials earlier, and followed up more carefully. For patients determined to be at high risk, hospitalization earlier than for patients at low risk may be suggested depending on the clinical course. Moreover, the publication of the prediction scores may be useful in educating the public. We

believe that these prediction scores based on age, sex, and comorbidity categorization represent a simple, easy-to-use, and helpful tool for primary care physicians and public health departments. If large databases, such as insurance databases, are available, prediction models appropriate for specific settings can be developed using the approach described in this study. Therefore, this methodology would be applicable to other diseases such as coronavirus disease 2019 and influenza in other regions.

In this study, anti-influenza drugs were prescribed to all patients on the date of influenza diagnosis, and pneumonia was diagnosed very often on the same day or within a few days of influenza diagnosis (Supplementary Figure 1A). Therefore, it is unlikely that the prescription of anti-influenza drugs significantly affected the incidence of early-onset pneumonia, although it may have reduced the incidence of late-onset pneumonia. Thus, our prediction model for pneumonia may also be applicable in countries where anti-influenza drugs are less commonly prescribed. By contrast, the time from influenza diagnosis to death varied considerably among patients (Supplementary Figure 1B). Therefore, a causal relationship between the prescription of anti-influenza drugs and mortality should be considered. Our prediction models, especially for death, may need further validation or modification to be more appropriate for other countries.

Published studies on hospitalized influenza patients show that about one-third of these patients develop pneumonia [12, 14], while a small population-based study, with ~1000 influenza cases, reported that 2.2% developed pneumonia [26]. However, pneumonia incidence in large population-based studies using data from thousands of patients has not been reported, and we show that, among >25 000 influenza cases, including outpatients, 2.9% developed pneumonia. Additionally, classification of patients by age revealed that the 28-day incidence of pneumonia increased with age and that it was particularly high among patients aged ≥75 years. This pattern is similar to that seen in community-acquired pneumonia wherein incidence increases with advancing age [27].

While chronic diseases have been reported as risk factors for serious complications in influenza [2, 16], such factors for pneumonia are not yet fully established. Even though several hospital-based studies have identified chronic respiratory disease and older age as relevant risk factors for pneumonia [14, 28], it remains unclear whether these risk factors are applicable to general populations because of the potential selection bias in those studies; specifically, patients admitted for influenza symptoms would be more likely to be already critically ill at the time of admission or to have a serious underlying disease. Our large-scale population-based study also determined that older age and chronic respiratory disease were independent risk factors for pneumonia, in addition to male gender, dementia, congestive heart failure, and diabetes.

The mortality rate in our main cohort was ~0.6%, and such relatively high mortality could be due to the high proportion of elderly people in the SKDB database. Therefore, we assessed mortality after classification by age and found that older age, that is, age ≥65 years, is associated with higher incidence of both pneumonia and death. Further, as patients aged ≥75 years showed considerably higher rates of pneumonia development and mortality compared with those aged <75 years, smaller age intervals are needed when classifying patients aged ≥65 years to better assess the risk of pneumonia and death in this population.

A hospital-based study with 754 influenza cases reported that each of the following comorbidities was a prognostic factor for death: congestive heart failure, diabetes, liver disease, malignancy, cerebrovascular disease, chronic kidney disease, and ischemic heart disease [29]. Similarly, our population-based study has also identified dementia, congestive heart failure, diabetes, liver disease, and metastatic solid tumor as independent prognostic factors for death. Notably, we also demonstrate that developing pneumonia carried a high risk of mortality, suggesting that prevention of pneumonia and its early diagnosis/treatment may play a pivotal role in reducing its mortality risk. In addition, incorporating pneumonia diagnosis and time to pneumonia diagnosis may improve our prediction model for death, which is a topic for future studies.

Nonetheless, this population-based study has several limitations. First, this study used information available in the insurance database, which does not record data on smoking, body mass index, pregnancy, severity of comorbidities, or influenza vaccination [30–32]. Second, the diagnosis of pneumonia in this study was based on ICD-10 codes and was not radiologically confirmed. Third, this database did not cover all residents in the Shizuoka prefecture, but we were able to minimize the impact of this bias by classifying the cohort by age and performing multivariate analysis. Fourth, even though external validation was conducted to assess the performance of these prediction scores, the data sets used were derived from the same database but from different years and may, therefore, not represent true external validation. Fifth, the causative pathogen of pneumonia was mostly unknown on the receipts, and accurate information could not be obtained. Sixth, the exact frequency of influenza-related hospitalizations could not be determined. Finally, there was a large difference in the total number of patients with influenza and overall mortality rates between the main cohort and validation cohort 1. The exact reason for this remains unclear, but could be due to differences in the virus strains prevalent during the influenza season. Nonetheless, we were able to successfully validate our prediction scores as we show comparable discrimination in both cohorts.

In conclusion, our large-scale, population-based study of adult patients with laboratory-confirmed influenza provides data on pneumonia incidence and mortality by age group, and this further demonstrates that older age and certain comorbidities were predictive of pneumonia and death, and influenza-associated pneumonia was associated with a substantial increase in mortality within 28 days of an influenza diagnosis. Based on these findings, we developed and successfully validated a simple-to-use prediction score system for influenza-related pneumonia

and death. Such an approach may be applicable to other cohorts or other prevalent diseases. We believe that the results of this study will not only contribute to our knowledge on the epidemiology of influenza, but also provide valuable information to clinicians in primary care settings.

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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Potential conflicts of interest. The authors declare that they have no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. K.M. and E.N. were equally contributing authors. K.M., E.N., H.H., Y.M., and T.S. conceived the study concept and drafted the manuscript. K.M., E.N., and Y.S. performed the analysis. All authors interpreted the results, revised the manuscript critically for important intellectual content, approved the final manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability. Data that support the findings of this study are available from the Shizuoka Prefectural National Health Insurance Association. However, restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available.

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