Association between Maoto Use and Hospitalization for Seasonal Influenza in a Nonelderly Cohort in Japan

Hayato Yamana¹, Sachiko Ono², Nobuaki Michihata¹, Taisuke Jo¹ and Hideo Yasunaga³

Abstract:
Objective Maoto is a traditional Japanese Kampo formula used to treat influenza. However, clinical evidence for maoto has been limited to small-scale studies of its effect in alleviating symptoms. The present study evaluated whether or not the addition of maoto to a neuraminidase inhibitor was associated with a reduction in hospitalization following influenza.
Methods Using the JMDC Claims Database, we identified outpatients <60 years old who were diagnosed with influenza by an antigen test from September 2013 to August 2018. One-to-five propensity score matching was conducted between patients who received maoto in addition to a neuraminidase inhibitor and those who received a neuraminidase inhibitor alone. Hospitalization within seven days of the influenza diagnosis was compared in the matched groups using the Mantel-Haenszel test.
Results We identified 1.79 million cases of influenza from the database in the 5-year study period. Maoto was prescribed for 3.9% of the 1.67 million cases receiving a neuraminidase inhibitor. In the 64,613 propensity score-matched groups of patients, the 7-day hospitalization rate was 0.116% (n=75) for patients with maoto and 0.122% (n=394) for patients without maoto. The difference between these treatment groups was nonsignificant (common odds ratio, 0.95; 95% confidence interval, 0.74 to 1.22; p=0.695).
Conclusion The addition of maoto to a neuraminidase inhibitor was not associated with a decrease in hospitalization among nonelderly patients with influenza. Further research is necessary to clarify the indication and efficacy of maoto.

Key words: complementary therapies, database, hospitalization, human influenza, Kampo medicine

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Introduction

Influenza is a common viral infectious disease, with 1 billion cases per year worldwide (1, 2). Each year, 3-5 million severe influenza cases and 290,000-650,000 influenza-associated deaths are estimated to occur (2, 3). Risk factors for severe influenza include age and chronic medical conditions, such as chronic lung disease, cardiovascular disease, neuromuscular disease, and diabetes (4-7). Studies have shown that neuraminidase inhibitors (NAIs) decrease the symptom duration and may reduce adverse outcomes (8, 9).

Maoto (Ma-Huang-Tang in Chinese) is a traditional Japanese Kampo formula used to treat the common cold and influenza. Maoto is made from ephedra herb, apricot kernel, cinnamon bark, and glycyrrhiza root. It is available for prescription as a granule or powder extract in the Japanese health insurance system. In vitro and in vivo studies have indicated the effects of maoto’s components in inhibiting the proliferation of influenza virus and provoking host reactions (10-15). Several small-scale clinical studies have evaluated maoto’s effect in alleviating the symptoms of influenza (16-20). A review of these studies concluded that adding maoto to an NAI was associated with a reduction in the duration of a fever (21).

However, previous studies on maoto’s efficacy for treating...
influenza have been from a small number of institutions. Thus, the recent use of maoto for treating influenza in general practice has not been described. In addition, existing clinical studies have had insufficient sample sizes to observe the occurrence of severe influenza cases. To our knowledge, no study on maoto has examined influenza-related mortality. In the few studies evaluating morbidity or hospitalization following influenza, no patients experienced complications or hospitalization (16, 17, 19, 20). Therefore, the effect of maoto on reducing adverse outcomes of influenza is unclear.

We conducted the present study to describe the use of maoto for the treatment of seasonal influenza. We further evaluated whether or not the addition of maoto to an NAI was associated with a reduction in hospitalization following influenza.

### Materials and Methods

#### Data source

We conducted a retrospective cohort study using the JMDC Claims Database (JMDC, Tokyo, Japan), a database of health insurance claims and health examinations in Japan. The database contains anonymous data provided by employer health insurance groups. Subscriber information includes the sex, year and month of birth, data provision period, and year and month of death. All monthly medical claims data on health insurance-covered outpatient, inpatient, and pharmacy services are recorded in the database, including diagnoses, consultations, drugs, and procedures. Diagnoses are recorded based on International Classification of Diseases, 10th Revision (ICD-10) codes and the Japanese standardized diagnosis codes. The date of treatment start for each diagnosis and whether the diagnosis was suspected or confirmed are also recorded. Drugs are classified according to the Anatomical Therapeutic Chemical Classification System and the Japanese codes for reimbursement. The date and institution of prescription are recorded in addition to the types and amounts of drugs prescribed. Procedures and their provision date are also recorded according to the Japanese codes for reimbursement.

#### Patients

Using the data recorded in the JMDC Claims Database from September 2013 to August 2018, we first identified the outpatient diagnosis records of confirmed influenza (ICD-10 code J10 or J11). For each subscriber, the earliest day within each one-year period (from September to August) that treatment for influenza started was considered the index date. Multiple cases in the same patient in different years were counted separately, whereas only the first episode for each patient within a 1-year period was included in the analysis. In this study, we included patients <60 years old. In Japan, upon retirement, individuals stop using company health insurance and are instead covered by citizens’ insurance. In addition, all people in Japan are covered by the Late Elders’ Health Insurance after they reach 75 years old (22). These people are not represented in the JMDC Claims Database. For inclusion in the analysis, we also required patients to have undergone an antigen test for influenza on the index date. Patients who did not receive an antigen test and those who received tests in multiple institutions were excluded.

#### Variables and outcomes

Using outpatient records for the same day a patient received antigen testing and at the same institution, we identified prescription of maoto, NAIs (oseltamivir, zanamivir, lanamivir, or peramivir) or baloxavir marboxil (a cap-dependent endonuclease inhibitor), and acetaminophen (oral or suppository). The type of influenza (A or B) was identified using the Japanese standardized diagnosis codes and categorized as unspecified when the diagnostic codes did not indicate specific influenza type or when both type A and type B were recorded. Using all confirmed diagnosis records from one to three months prior to the influenza diagnosis, the following comorbidities were identified: chronic heart failure, myocardial infarction, chronic pulmonary diseases, liver diseases, diabetes mellitus, and renal diseases. The diagnoses and their codes were based on Quan et al.’s algorithm for calculating the Charlson comorbidity index (23). We also identified whether or not a patient had been hospitalized for any reason during the month preceding the influenza diagnosis. Finally, the total outpatient charge during the previous month was calculated as a measure of baseline service utilization.

The primary study outcome was all-cause hospitalization within seven days after the influenza diagnosis. Among patients who were hospitalized, we used the diagnosis records to identify pneumonia, encephalopathy and encephalitis, otitis media, and any diseases of the respiratory system. Furthermore, we used procedure records during hospitalization to capture intensive-care unit admission, instances of intratracheal intubation, and electroencephalograms. Death from any cause in the month of the influenza diagnosis was also identified.

#### Statistical analyses

For each year, the number of influenza cases occurring each week was counted. Because the number of subscribers for whom data were provided varied by year, epidemic curves were drawn after adjusting for total person-months observed in the database each year.

The characteristics of influenza cases were described using proportions for categorical variables and means with standard deviations for continuous variables. The proportions of patients who had complications and who died were calculated among patients hospitalized within seven days after the influenza diagnosis.

We conducted a comparative analysis using propensity score matching in patients who received one type of NAI. Patients who did not receive NAIs and those who received
multiple antiviral agents were excluded from this analysis. Propensity scores were estimated using logistic regression, with use of maoto in addition to an NAI set as the dependent variable. Sex, age, year, type of influenza, type of NAI, acetaminophen use, comorbidities (congestive heart failure, chronic pulmonary disease, liver disease, diabetes, and renal disease), hospitalization during the previous month, and total outpatient charge during the previous month (none, ≤12,000 yen, or >12,000 yen) were included as independent variables. Using the estimated propensity scores, we performed nearest-neighbour one-to-five matching with replacement between patients who received maoto in addition to an NAI and patients who received an NAI alone. The cut-off for a difference in propensity score was set at 0.2 times the standard deviation of the estimated propensity scores. Covariates for which the absolute value of the standardized difference exceeded 10% were considered imbalanced between the two groups (24).

Mantel-Haenszel test with stratification by the matched groups was used to compare rates of hospitalization within seven days after the influenza diagnosis between patients with and without maoto. As a sensitivity analysis, we compared the 14-day admission rate in the same manner. We conducted subgroup analyses by performing propensity score matching in each subgroup for sex, age group, type of influenza, type of NAI, and acetaminophen use. P<0.05 was considered statistically significant. Statistical analyses were performed using the Stata SE software program, Version 16.0 (StataCorp, College Station, USA).

**Ethical considerations**

The study was approved by the Institutional Review Board of the Graduate School of Medicine, The University of Tokyo. The requirement for informed consent was waived because of the anonymous nature of the data.

**Results**

We identified 1,993,639 influenza cases using diagnosis records during the 5-year study period. Of these cases, 195,156 without antigen tests and 4,119 with antigen tests in multiple institutions were excluded. The number of included cases, incidence, age distribution, and type of influenza in each year are presented in Table 1. The highest incidence of influenza was observed in 2017-18. The epidemic curves for each year after adjusting for the observation period are presented in Figure.

Table 2 describes the number of hospitalized patients by their use of antiviral agents and maoto. Overall, maoto was prescribed for 72,136 patients (4.0%). Of the 1,794,364 patients, 2,782 (0.16%) were hospitalized within 7 days after the influenza diagnosis, and an additional 1,341 were hospitalized 8-14 days after the influenza diagnosis. There were 15 deaths in the month of the influenza diagnosis (0.001%). The 2,782 patients hospitalized within 7 days after the influenza diagnosis included 615 (22%) with pneumonia, 39 (1.4%) with encephalopathy, and 51 (1.8%) with otitis media. There were 29 patients (1.0%) who required intensive-care unit admission, and 36 patients (1.3%) were intubated. An electroencephalogram was performed in 67 patients (2.4%).

There were 3,135, 736, and 118,752 patients who received baloxavir marboxil, multiple types of antiviral agents, and no NAIs, respectively. The characteristics of the remaining 1,671,741 patients who received one type of NAI and the results of univariate analyses for hospitalization within 7 days after the influenza diagnosis are presented in Table 3. The mean age was 23.9 years old, with a standard deviation

### Table 1. Influenza Cases Identified in the JMDC Claims Database.

| Year       | 2013-14 | 2014-15 | 2015-16 | 2016-17 | 2017-18 |
|------------|---------|---------|---------|---------|---------|
| Observed population (in millions) | 2.75    | 3.65    | 4.19    | 4.79    | 4.88    |
| Influenza cases (n) | 217,977 | 242,996 | 356,559 | 412,167 | 564,665 |
| Influenza incidence (/1,000 person-years) | 91.0 | 86.6 | 102.6 | 104.6 | 135.5 |

| Patient characteristics, n (%) |
|--------------------------------|
| Sex |
|   Male | 121,533 (56) | 134,436 (55) | 196,895 (55) | 225,172 (55) | 308,549 (55) |
|   Female | 96,444 (44) | 108,560 (45) | 159,664 (45) | 186,995 (45) | 256,116 (45) |
| Age group, years |
|   0-9 | 67,596 (31) | 65,628 (27) | 108,074 (30) | 102,264 (25) | 153,559 (27) |
|   10-19 | 51,113 (23) | 62,769 (26) | 83,323 (23) | 110,055 (27) | 138,800 (25) |
|   20-39 | 53,413 (25) | 60,448 (25) | 77,569 (22) | 98,861 (24) | 117,278 (21) |
|   40-59 | 45,855 (21) | 54,151 (22) | 87,593 (25) | 100,987 (25) | 155,028 (27) |
| Type of influenza |
|   A | 70,809 (32) | 139,882 (58) | 105,141 (29) | 243,473 (59) | 141,384 (25) |
|   B | 59,352 (27) | 10,344 (4) | 119,843 (34) | 25,513 (6) | 233,603 (41) |
|   Unspecified | 87,816 (40) | 92,770 (38) | 131,575 (37) | 143,181 (35) | 189,678 (34) |
of 17.0 years. Maoto was prescribed for 64,613 patients (3.9%) in this group.

Through propensity score matching, 323,065 patients without maoto were selected as matched counterparts for patients with maoto, all of whom were included in the analysis. There were no patients with missing data. Comparisons of patient characteristics between those who received maoto and those who did not before and after propensity score matching are presented in Table 4. Patient characteristics were well-balanced after matching.

Within the 64,613 matched groups of 1 patient with maoto and 5 patients without maoto, the 7-day admission rate was 0.116% (n=75) for patients with maoto and 0.122% (n=394) for patients without maoto. The risk difference was -0.006% [95% confidence interval (CI), -0.224% to 0.212%]. Mantel-Haenszel test showed no significant difference in admission rates (odds ratio, 0.95; 95% CI, 0.74 to 1.22; p=0.695). The 14-day admission rate was 0.184% (n=119) for patients with maoto and 0.166% (n=535) for patients without maoto. The risk difference was 0.019% (95% CI, -0.258% to 0.296%). The Mantel-Haenszel test again indicated no significant difference in admission rates (odds ratio, 1.11; 95% CI, 0.91 to 1.36; p=0.293).

The results of the subgroup analyses are summarized in Tables 5 and 6. Maoto use was associated with a higher rate of hospitalization in men than in women and a lower rate of hospitalization in women than in men. In addition, patients with maoto had higher hospitalization rates than those without maoto in the subgroup that received acetaminophen and the subgroup that received laninamivir.

Discussion

Using a large-scale health insurance claims database in Japan, we investigated the use of maoto for treating seasonal influenza and evaluated whether or not the addition of maoto to an NAI was associated with a reduction in hospitalizations. Maoto was used in 4% of the included influenza

Table 2. Use of Antiviral Agents and Maoto and Hospitalization Status.

| Antiviral agent use | Maoto use | n   | Hospitalization within 7 days | n   | (% ) | Hospitalization within 14 days | n   | (%) |
|---------------------|-----------|-----|-------------------------------|-----|------|-------------------------------|-----|------|
| + +                 | 64,809    | 75  | (0.12)                        | 119 | (0.18) |
| + -                 | 1,610,803 | 2,124| (0.13)                        | 3,268| (0.20)  |
| - +                 | 7,327     | 27  | (0.37)                        | 34  | (0.46)  |
| - -                 | 111,425   | 556 | (0.50)                        | 702 | (0.63)  |
| Total               | 1,794,364 | 2,782| (0.16)                        | 4,123| (0.23)  |

Figure. Weekly cases of influenza identified from the JMDC Claims Database. The number of cases in each year is adjusted to the average population of 4.05 million subscribers contributing 3.36 million person-years of observation.
Table 3. Patient Characteristics and Results of Univariate Analyses (n=1,671,741).

| Characteristic                  | Total, n | Hospitalization within 7 days, n (%) | p    |
|--------------------------------|----------|-------------------------------------|------|
|                                |          |                                     |      |
| Sex                            |          |                                     |      |
| Male                           | 918,637  | 1,174 (0.13)                        | 0.198|
| Female                         | 753,104  | 1,017 (0.14)                        |      |
| Age group, years               |          |                                     |      |
| 0-9                            | 457,652  | 847 (0.19)                          | <0.001|
| 10-19                          | 420,774  | 395 (0.09)                          |      |
| 20-39                          | 376,298  | 404 (0.11)                          |      |
| 40-59                          | 417,017  | 545 (0.13)                          |      |
| Year                           |          |                                     |      |
| 2013-14                        | 201,543  | 282 (0.14)                          | <0.001|
| 2014-15                        | 226,797  | 249 (0.11)                          |      |
| 2015-16                        | 331,791  | 537 (0.16)                          |      |
| 2016-17                        | 386,227  | 445 (0.12)                          |      |
| 2017-18                        | 525,383  | 678 (0.13)                          |      |
| Type of influenza              |          |                                     |      |
| A                              | 677,469  | 822 (0.12)                          | <0.001|
| B                              | 431,848  | 544 (0.13)                          |      |
| Unspecified                    | 562,424  | 825 (0.15)                          |      |
| Neuraminidase inhibitor        |          |                                     |      |
| Oseltamivir                    | 560,259  | 941 (0.17)                          | <0.001|
| Zanamivir                      | 261,396  | 302 (0.12)                          |      |
| Lamivudine                     | 809,968  | 818 (0.10)                          |      |
| Peramivir                      | 40,118   | 110 (0.32)                          |      |
| Acetaminophen use              |          |                                     |      |
| Yes                            | 1,177,143| 1,471 (0.12)                        | 0.001|
| No                             | 494,598  | 720 (0.15)                          |      |
| Maoto use                      |          |                                     |      |
| Yes                            | 64,613   | 75 (0.12)                           | 0.283|
| No                             | 1,607,128| 2,116 (0.13)                        |      |
| Congestive heart failure       |          |                                     |      |
| Yes                            | 7,588    | 51 (0.67)                           | <0.001|
| No                             | 1,664,153| 2,140 (0.13)                        |      |
| Chronic pulmonary disease      |          |                                     |      |
| Yes                            | 232,032  | 589 (0.25)                          | <0.001|
| No                             | 1,439,709| 1,602 (0.11)                        |      |
| Liver disease                  |          |                                     |      |
| Yes                            | 30,423   | 82 (0.27)                           | <0.001|
| No                             | 1,641,318| 2,109 (0.16)                        |      |
| Diabetes                       |          |                                     |      |
| Yes                            | 6,492    | 37 (0.57)                           | <0.001|
| No                             | 1,665,249| 2,154 (0.13)                        |      |
| Renal disease                  |          |                                     |      |
| Yes                            | 2,732    | 22 (0.81)                           | <0.001|
| No                             | 1,669,009| 2,169 (0.13)                        |      |
| Hospitalization in previous month |        |                                     |      |
| Yes                            | 5,135    | 63 (1.23)                           | <0.001|
| No                             | 1,666,606| 2,128 (0.13)                        |      |
| Outpatient charge in previous month, yen |    |                                     |      |
| None                           | 1,016,353| 889 (0.09)                          | <0.001|
| ≤12,000                        | 355,029  | 469 (0.13)                          |      |
| >12,000                        | 300,359  | 833 (0.28)                          |      |
ever, the use of Kampo formulations with a Western diagnosis is increasing, and clinical studies based on Western diagnoses have been conducted (28). A possible reason for the nonsignificant effect in this study is that patients may have been prescribed maoto against their symptoms, further research using traditional diagnoses is necessary to evaluate whether or not maoto is effective in patients with the correct indication.

Several study limitations must be acknowledged. First, this study used health insurance claims data. Detailed information on severity and underlying diseases was not available. Second, this was a retrospective observational study. Although we conducted propensity score matching to adjust for multiple measured confounding factors, unmeasured confounders, such as the vaccination status, may have affected the findings. Finally, the study did not include older adult patients. The results may not be generalizable to patients of older age because hospitalization is more frequent in this group than in younger patients, and older adult patients more frequently have conditions preventing the use of maoto, such as cardiovascular diseases and prostate hypertrophy, than younger patients.

In conclusion, the addition of maoto to an NAI was not associated with a decrease in hospitalization among nonelderly patients with seasonal influenza. Further research is necessary to clarify the indication and efficacy of maoto.

**Author’s disclosure of potential Conflicts of Interest (COI).**

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### Table 4. Patient Characteristics before and after Propensity Score Matching.

| Characteristic                        | Patients with maoto, n=64,613 (%) | Patients without maoto (all), n=1,607,128 (%) | Standardized difference<sup>a</sup> | Patients without maoto (matched), n=323,065 (%) | Standardized difference<sup>b</sup> |
|---------------------------------------|-----------------------------------|---------------------------------------------|-------------------------------------|-----------------------------------------------|-------------------------------------|
| Male                                  | 37,983 (58.8)                     | 880,654 (54.8)                              | 8.06                                | 189,777 (58.7)                               | 0.09                                |
| Age group, years                      |                                   |                                             |                                     |                                               |
| 0-9                                   | 4,578 (7.1)                       | 453,074 (28.2)                              | -57.63                              | 22,918 (7.1)                                 | -0.03                               |
| 10-19                                 | 12,440 (19.3)                     | 408,334 (25.4)                              | -14.82                              | 62,227 (19.3)                                | -0.02                               |
| 20-39                                 | 22,662 (35.1)                     | 353,636 (22.0)                              | 29.25                               | 113,322 (35.1)                               | -0.01                               |
| 40-59                                 | 24,933 (38.6)                     | 392,084 (24.4)                              | 30.92                               | 124,598 (38.6)                               | 0.04                                |
| Year                                  |                                   |                                             |                                     |                                               |
| 2013-14                               | 6,934 (10.7)                      | 194,609 (12.1)                              | -4.33                               | 34,636 (10.7)                                | 0.03                                |
| 2014-15                               | 8,223 (12.7)                      | 218,574 (13.6)                              | -2.58                               | 41,176 (12.7)                                | -0.06                               |
| 2015-16                               | 12,496 (19.3)                     | 319,295 (19.9)                              | -1.33                               | 62,556 (19.4)                                | -0.06                               |
| 2016-17                               | 16,107 (24.9)                     | 370,120 (23.0)                              | 4.45                                | 80,364 (24.9)                                | 0.12                                |
| 2017-18                               | 20,853 (32.3)                     | 504,530 (31.4)                              | 1.89                                | 104,333 (32.3)                               | -0.05                               |
| Type of influenza                     |                                   |                                             |                                     |                                               |
| A                                     | 29,173 (45.2)                     | 648,296 (40.3)                              | 9.74                                | 145,859 (45.1)                               | 0.00                                |
| B                                     | 15,536 (24.0)                     | 416,312 (25.9)                              | -4.30                               | 77,676 (24.0)                                | 0.00                                |
| Unspecified                           | 19,904 (30.8)                     | 542,520 (33.8)                              | -6.32                               | 99,530 (30.8)                                | -0.01                               |
| Neuraminidase inhibitor               |                                   |                                             |                                     |                                               |
| Oseltamivir                           | 12,339 (19.1)                     | 547,920 (34.1)                              | -34.44                              | 61,739 (19.1)                                | -0.03                               |
| Zanamivir                             | 7,201 (11.1)                      | 254,195 (15.8)                              | -13.71                              | 35,958 (11.1)                                | 0.05                                |
| Laninamivir                           | 41,371 (64.0)                     | 768,597 (47.8)                              | 33.08                               | 206,814 (64.0)                               | 0.03                                |
| Peramivir                             | 3,702 (5.7)                       | 36,416 (2.3)                                | 17.75                               | 18,554 (5.7)                                 | -0.06                               |
| Acetaminophen use                     | 48,068 (74.4)                     | 1,129,075 (70.3)                            | 9.26                                | 240,290 (74.4)                               | 0.04                                |
| Congestive heart failure              | 371 (0.6)                         | 7,217 (0.4)                                 | 1.75                                | 1,513 (0.5)                                  | 1.47                                |
| Chronic pulmonary disease             | 5,750 (8.9)                       | 226,282 (14.1)                              | -16.30                              | 28,775 (8.9)                                 | -0.03                               |
| Liver disease                         | 1,740 (2.7)                       | 28,683 (1.8)                                | 6.14                                | 8,340 (2.6)                                  | 0.70                                |
| Diabetes                              | 352 (0.5)                         | 6,140 (0.4)                                 | 2.40                                | 1,499 (0.5)                                  | 1.16                                |
| Renal disease                         | 134 (0.2)                         | 2,598 (0.2)                                 | 1.07                                | 426 (0.1)                                    | 1.84                                |
| Hospitalization in previous month     | 180 (0.3)                         | 4,955 (0.3)                                 | -0.55                               | 691 (0.2)                                    | 1.31                                |
| Outpatient charge in previous month, yen |                                   |                                             |                                     |                                               |
| None                                  | 41,723 (64.6)                     | 974,630 (60.6)                              | 8.13                                | 208,710 (64.6)                               | -0.06                               |
| ≤12,000                               | 11,895 (18.4)                     | 343,134 (21.4)                              | -7.37                               | 59,509 (18.4)                                | -0.03                               |
| >12,000                               | 10,995 (17.0)                     | 289,364 (18.0)                              | -2.60                               | 54,846 (17.0)                                | 0.11                                |

Every patient in the maoto group was matched with five patients without maoto.

<sup>a</sup>Between patients with maoto and all patients without maoto.

<sup>b</sup>Between patients with maoto and matched patients without maoto.
**Table 5. Result of Subgroup Analysis for Hospitalization within 7 Days.**

| Subgroup                              | Patients with maoto Matched, n | Hospitalized n (%) | Patients without maoto Matched, n | Hospitalized n (%) | Odds ratio | 95% CI      | p   |
|---------------------------------------|---------------------------------|--------------------|-----------------------------------|--------------------|------------|-------------|-----|
| **Sex**                               |                                 |                    |                                   |                    |            |             |     |
| Male                                  | 37,983                          | 42 (0.11)          | 189,915                          | 122 (0.06)         | 1.73       | (1.21, 2.46) | 0.002|
| Female                                | 26,630                          | 33 (0.12)          | 133,150                          | 268 (0.20)         | 0.61       | (0.43, 0.88) | 0.008|
| **Age group, years**                  |                                 |                    |                                   |                    |            |             |     |
| 0-9                                   | 4,578                           | 7 (0.15)           | 22,890                           | 30 (0.13)          | 1.17       | (0.51, 2.66) | 0.713|
| 10-19                                 | 12,440                          | 11 (0.09)          | 62,199                           | 144 (0.23)         | 0.38       | (0.21, 0.71) | 0.001|
| 20-39                                 | 22,662                          | 23 (0.10)          | 113,310                          | 160 (0.14)         | 0.72       | (0.46, 1.11) | 0.137|
| 40-59                                 | 24,933                          | 34 (0.14)          | 124,665                          | 83 (0.07)          | 2.07       | (1.38, 3.11) | <0.001|
| **Type of influenza**                 |                                 |                    |                                   |                    |            |             |     |
| A                                     | 29,173                          | 22 (0.08)          | 145,865                          | 102 (0.07)         | 1.08       | (0.68, 1.71) | 0.747|
| B                                     | 15,536                          | 14 (0.09)          | 77,680                           | 37 (0.05)          | 1.89       | (1.02, 3.50) | 0.039|
| Unspecified                           | 19,940                          | 39 (0.20)          | 99,520                           | 114 (0.11)         | 1.72       | (1.19, 2.47) | 0.003|
| Neuraminidase inhibitor               |                                 |                    |                                   |                    |            |             |     |
| Oseltamivir                           | 12,339                          | 20 (0.16)          | 61,695                           | 75 (0.12)          | 1.34       | (0.81, 2.22) | 0.249|
| Zanamivir                             | 7,201                           | 3 (0.04)           | 36,005                           | 31 (0.09)          | 0.48       | (0.15, 1.58) | 0.220|
| Laninamivir                           | 41,371                          | 45 (0.11)          | 206,855                          | 61 (0.03)          | 3.69       | (2.51, 5.42) | <0.001|
| Peramivir                             | 3,702                           | 7 (0.19)           | 18,510                           | 22 (0.12)          | 1.59       | (0.68, 3.72) | 0.280|
| Acetaminophen use                     |                                 |                    |                                   |                    |            |             |     |
| Yes                                   | 48,068                          | 63 (0.13)          | 240,340                          | 111 (0.05)         | 2.84       | (2.08, 3.87) | <0.001|
| No                                    | 16,545                          | 12 (0.07)          | 82,725                           | 82 (0.10)          | 0.73       | (0.40, 1.34) | 0.310|

CI: confidence interval

**Table 6. Result of Subgroup Analysis for Hospitalization within 14 Days.**

| Subgroup                              | Patients with maoto Matched, n | Hospitalized n (%) | Patients without maoto Matched, n | Hospitalized n (%) | Odds ratio | 95% CI      | p   |
|---------------------------------------|---------------------------------|--------------------|-----------------------------------|--------------------|------------|-------------|-----|
| **Sex**                               |                                 |                    |                                   |                    |            |             |     |
| Male                                  | 37,983                          | 66 (0.17)          | 189,915                          | 176 (0.09)         | 1.88       | (1.42, 2.50) | <0.001|
| Female                                | 26,630                          | 53 (0.20)          | 133,150                          | 354 (0.27)         | 0.75       | (0.56, 1.00) | 0.048|
| **Age group, years**                  |                                 |                    |                                   |                    |            |             |     |
| 0-9                                   | 4,578                           | 9 (0.20)           | 22,890                           | 37 (0.16)          | 1.22       | (0.59, 2.52) | 0.598|
| 10-19                                 | 12,440                          | 13 (0.10)          | 62,199                           | 152 (0.24)         | 0.43       | (0.24, 0.75) | 0.003|
| 20-39                                 | 22,662                          | 36 (0.16)          | 113,310                          | 241 (0.21)         | 0.75       | (0.53, 1.06) | 0.101|
| 40-59                                 | 24,933                          | 61 (0.24)          | 124,665                          | 178 (0.14)         | 1.73       | (1.29, 2.32) | <0.001|
| **Type of influenza**                 |                                 |                    |                                   |                    |            |             |     |
| A                                     | 29,173                          | 41 (0.14)          | 145,865                          | 204 (0.14)         | 1.00       | (0.72, 1.41) | 0.977|
| B                                     | 15,536                          | 21 (0.14)          | 77,680                           | 59 (0.08)          | 1.79       | (1.08, 2.97) | 0.021|
| Unspecified                           | 19,940                          | 57 (0.29)          | 99,520                           | 186 (0.19)         | 1.54       | (1.14, 2.07) | 0.004|
| Neuraminidase inhibitor               |                                 |                    |                                   |                    |            |             |     |
| Oseltamivir                           | 12,339                          | 30 (0.24)          | 61,695                           | 275 (0.45)         | 0.54       | (0.37, 0.79) | 0.001|
| Zanamivir                             | 7,201                           | 8 (0.11)           | 36,005                           | 60 (0.17)          | 0.67       | (0.32, 1.39) | 0.278|
| Laninamivir                           | 41,371                          | 71 (0.17)          | 206,855                          | 98 (0.05)          | 3.65       | (2.68, 4.96) | <0.001|
| Peramivir                             | 3,702                           | 10 (0.27)          | 18,510                           | 37 (0.20)          | 1.35       | (0.67, 2.72) | 0.396|
| Acetaminophen use                     |                                 |                    |                                   |                    |            |             |     |
| Yes                                   | 48,068                          | 95 (0.20)          | 240,340                          | 241 (0.10)         | 1.97       | (1.56, 2.50) | <0.001|
| No                                    | 16,545                          | 24 (0.15)          | 82,725                           | 154 (0.19)         | 0.78       | (0.50, 1.20) | 0.253|

CI: confidence interval
Tsunura. Taisuke Jo: Others, Tsunurma. Sachiko Ono: Others, ITO EN.

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