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Prompt Oseltamivir Therapy Reduces Medical Care and Mortality for Patients With Influenza Infection

An Asian Population Cohort Study

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Abstract: There are limited population-based studies on the progress of oseltamivir therapy for influenza infection.

Using insurance claims data of 2005, 2009, and 2010, the authors established an ''in-time'' cohort and a ''lag-time'' cohort representing influenza patients taking the medicine within and not within 1 week to examine the treatment progress. Incident outpatient visit, emergency care and hospitalization, and fatality were compared between the 2 cohorts in the first week and the second week of follow-up periods, after the oseltamivir therapy.

A total of 112,492 subjects diagnosed with influenza on oseltamivir therapy in 2005, 2009, and 2010 were identified. The multivariate logistic regression analysis showed that the in-time treatment was superior to the lag-time treatment with less repeat outpatient visits, hospitalizations, and fatality. The overall corresponding in-time treatment to lag-time treatment odds ratios (OR) were 0.50, 0.54, and 0.71 (all P value < 0.05), respectively. The in-time to lag-time ORs of all events were 0.50 in 2009 and 0.54 in 2010.

Our study demonstrates that the in-time oseltamivir therapy leads to significantly better treatment outcomes. Oseltamivir should be administered as early as the onset of influenza symptoms appears.

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Abbreviations: ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, OR and 95% CI = odds ratio and 95% confidence interval, USCDC = US Centers for Disease Control and Prevention, WHO = World Health Organization.

INTRODUCTION

Oseltamivir and zanamivir are drugs recommended by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (USCDC) are the first-line antiviral drug for patients infected with influenza A and B.[1–3] The WHO guidelines recommended that patients with diagnosed or suspected influenza should be treated with antiviral medicine as soon as possible.[2] The USCDC also recommended to treat patients with confirmed or suspected influenza with antiviral agents as soon as possible.[3] Previous studies on the efficacy of antiviral medication used randomized controlled trials targeting patients with laboratory confirmed influenza infection.[4–6] The study results consistently support that oseltamivir is clinically effective for the treatment of influenza and further for the prevention of pneumonia.[4–6] Oseltamivir may provide symptomatic relief for patients with influenza infection, reduce viral excretion from the nose, and interrupt the household viral transmission. In addition, oseltamivir reduces the symptoms of flu, antibiotic uses, complications such as bronchitis and pneumonia, and death.[7–13] The oseltamivir treatment may reduce nearly 60% of the secondary spread of influenza in family members who have contacted with the patient.[14]

An estimated 45 million patients have received the antiviral treatment worldwide by 2013, since 2005.[15] A retrospective

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cohort study using a large health data of the US found that oseltamivir treatment twice daily could reduce pneumonia risk by 32%.[14] A hospital-based study has proved that the oseltamivir treatment effectiveness for patients receiving treatment in time is superior than the patients with delayed antiviral administration.[16]

Although oseltamivir is known as an effective medicine for influenza treatment, comparing outcomes and adverse responses between prompt initiation and delayed antiviral administration of this medicine has not been well examined for Asian population. This study took the advantage of population data available in the Taiwan's National Health Insurance to perform a retrospective cohort study. We evaluated the efficacy of oseltamivir therapy for patients diagnosed with influenza infection. Patients with oseltamivir therapy within 1 week were compared to those with the therapy beyond 1 week for treatment progress, evaluated by additional outpatient visits, emergency uses, hospitalization, and mortality during a 2-week follow-up period.

METHODS

Database

This study used claims data of the National Health Insurance Research Dataset (NHIRD) from 2000 to 2010, provided by the National Health Research Institutes in Taiwan. This large and comprehensive population-based health data set covers over 23,275,000 people in Taiwan. The diagnoses were coded with the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) for insurance claims registered. This study was approved by the research ethics committee at China Medical University and Hospital.

Study Cohorts and Outcomes Observation

We identified all adult patients with the principal diagnosis of influenza (ICD-9-CM480–487) and prescription of oseltamivir during influenza seasons in 2005, 2009, and 2010 (Figure 1). This medicine was used in 2005 for an influenza prevention trial mainly for the elderly diagnosed with influenza, and has been implemented for all eligible patients since 2009. From the prescription records available in the claims data, we ascertained the usage of oseltamivir for the specific date, dose, and route of every prescription in years 2005, 2009, and 2010. The date a patient initiated with the oseltamivir prescription was designated as the index day. Patients clinically newly diagnosed with influenza by physician and initiated the oseltamivir prescription within 1 week were designated into the in-time cohort. Patients who were diagnosed with influenza and started taking oseltamivir beyond 1 week of the diagnosis were designated as the lag-time cohort. We traced all patients prescribed with oseltamivir for a 2-week follow-up period, to observe the treatment progress, using additional outpatient visit, emergency use, hospitalization, and death as study outcomes. The first period (week 1) was from the eighth day to the 14th day following the oseltamivir prescription. The week 2 period began immediately after the completion of the preceding week 1 follow-up (ie, from the 15th day to 21st day). A 2-week follow-up period was designed to observe a short-term progress of the treatments. Patients who had taken oseltamivir and sought further medical services, including outpatient visit, emergency use or hospitalization, or had encountered death were identified weekly from the claims data during the 2-week follow-up period. These events were designated as adverse progressions.

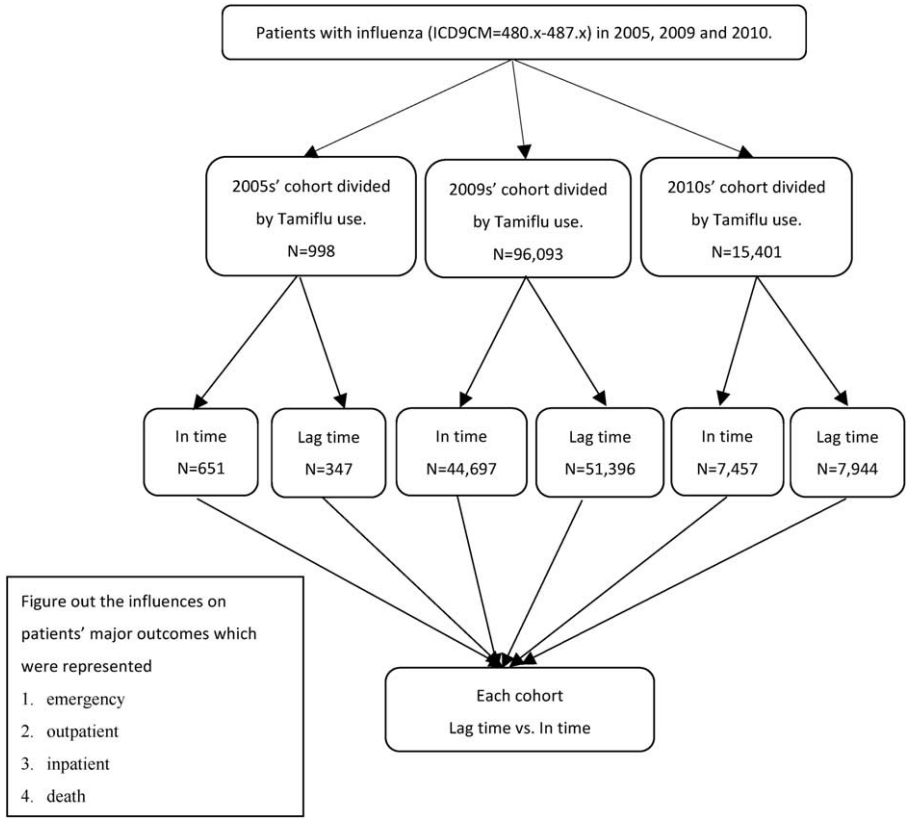

FIGURE 1. Flow chart of study design.

Statistical Analysis

Based on dates with influenza diagnosed and oseltamivir prescribed, patients were divided into "in-time" and "lag-time" cohorts, by the study year of 2005, 2009, and 2010. To determine whether patient characteristics were similar between the 2 prescription times for oseltamivir, we compared distributions of sex and age. The 2-week follow-up period-specific frequencies of outpatient visit, emergency use, hospitalization, and death were calculated for oseltamivir users in the in-time cohort and the lag-time cohort by study year. We used the Mantel-Haenszel method to calculate the in-time cohort to lag-time cohort odds ratio (OR) and 95% confidence interval (CI) of each event. We further used the multivariable logistic regression model to estimate the ORs of repeat outpatient visits, hospitalization, and death associated with in-time and lag-time treatments by age and sex in all 3 years combined. Similar data analysis method was also performed to estimate ORs of all events combined for 2009 and 2010 to evaluate whether the treatment effectiveness changed in 2010. The SAS software for Windows, Version 9.3 (SAS Institute Inc., Cary, NC) was used for data analyses with the 2-sided *P* value of 0.05 considered statistically significant.

RESULTS

Among patients clinically diagnosed with influenza, there were 998 cases in 2005, 96,093 cases in 2009, and 15,401 cases in 2010 on the oseltamivir therapy (Table 1). Influenza patients in 2005 were much older than those in 2009 and 2010. There were more in-time therapy patients than lag-time therapy patients in 2005, but not in 2009 and 2010. After taking the medicine, outpatient visits declined weekly. The outpatient visits in week 1 follow-up were 3.2-fold more frequent in the lag-time cohort than in the in-time cohort (32.3 versus 9.98%) in 2005. The difference in outpatient visits between the lag-time cohort and the in-time cohort was reduced in 2009 (26.3 versus 15.4%, respectively) and in 2010 (28.8 versus 17.9%, respectively). Similar trends remained in week 2 follow-up. The incidences of hospitalization and the mortality were lower in the in-time cohort than in the lag-time cohort during the 2-week period. The hospitalization rate and mortality were greater in 2005.

Among patients with oseltamivir therapy in the 3 years combined, 9502 (18.0%) in the in-time cohort and 18,174 (30.4%) in the lag-time cohort had repeat outpatient visits (Table 2). The Cochran-Mantel-Haenszel analysis estimated overall OR of repeat outpatient visits in patients with in-time therapy was 0.50 (95% CI = 0.49–0.52, $P < 0.0001$), comparing to lag-time therapy. The corresponding ORs of hospitalization and death for patients with in-time therapy were 0.54 (95% CI = 0.37–0.62, $P < 0.0001$) and 0.71(95% CI = 0.56–0.91, $P < 0.0001$), respectively. The oseltamivir therapy was consistently superior in the in-time cohort than in the lag-time cohort among study years, age groups, and both sexes. The age-specific results showed that the OR decreased as age increased, from 0.60 (95% CI = 0.58–0.63, $P < 0.0001$) in 20 to 29 years old to 0.34 (95% CI = 0.29–0.41, $P < 0.0001$) in 70 to 79 years old. The age-specific OR pattern of repeat outpatient visits, however, did not appear in hospitalization and death. The reduction

TABLE 1. Baseline Characteristics of Patients Among 3 Cohorts

	2005		2009		2010	
	In Time N = 651	**Lag Time N = 347**	**In Time N = 44,697**	**Lag Time N = 51,396**	**In Time N = 7,457**	**Lag Time N = 7,944**
Age	63.97 ± 19.95	62.27 ± 20.30	35.65 ± 13.47	35.96 ± 13.52	37.58 ± 15.26	38.52 ± 15.86
20–29	73 (11.21)	44 (12.68)	19469 (43.56)	21542 (41.91)	2993 (40.14)	3022 (38.04)
30–39	45 (6.91)	26 (7.49)	11071 (24.77)	13638 (26.54)	1993 (26.73)	2134 (26.86)
40–49	33 (5.07)	29 (8.36)	7818 (17.49)	8718 (16.96)	1047 (14.04)	1078 (13.57)
50–59	44 (6.76)	14 (4.03)	3868 (8.65)	4423 (8.61)	713 (9.56)	834 (10.50)
60–69	110 (16.90)	60 (17.29)	1305 (2.92)	1580 (3.07)	337 (4.52)	386 (4.86)
70–79	228 (35.02)	118 (34.01)	712 (1.59)	974 (1.90)	215 (2.88)	285 (3.59)
>=80	118 (18.13)	56 (16.14)	454 (1.02)	521 (1.01)	159 (2.13)	205 (2.58)
Gender						
Men	386 (59.29)	238 (68.59)	21620 (48.37)	21433 (41.70)	3597 (48.24)	3451 (43.44)
Women	265 (40.71)	109 (31.41)	23077 (51.63)	29963 (58.30)	3860 (51.76)	4493 (56.56)
Number of Outpatient Visits After the Index Day						
Week 1	65 (9.98)	112 (32.28)	6899 (15.44)	13520 (26.31)	1333 (17.88)	2285 (28.76)
Week 2	53 (8.14)	99 (28.53)	3523 (7.88)	8252 (16.06)	765 (10.26)	1530 (19.26)
Number of Emergency After the Index Day						
Week 1	0 (0.00)	0 (0.00)	6 (0.01)	5 (0.01)	0 (0.00)	0 (0.00)
Week 2	1 (0.15)	0 (0.00)	1 (0.00)	4 (0.01)	1 (0.01)	1 (0.01)
Number of Inpatient After the Index Day						
Week 1	0 (0.00)	2 (0.58)	43 (0.10)	103 (0.20)	16 (0.21)	26 (0.33)
Week 2	2 (0.31)	1 (0.29)	16 (0.04)	50 (0.10)	6 (0.08)	14 (0.18)
Number of Death After the Index Day						
Week 1	0 (0.00)	3 (0.86)	53 (0.12)	85 (0.17)	26 (0.35)	35 (0.44)
Week 2	2 (0.31)	0 (0.00)	12 (0.03)	32 (0.06)	11 (0.15)	10 (0.13)

Note: the P values for distribution variations were <0.0001 in age, gender and outpatient visits, 0.25 in emergency visit, 0.01 in inpatient care and 0.006 in death.

TABLE 2. Cochran-Mantel-Haenszel Analysis Estimated Odds Ratio of Events for 3-Year Combined In-Time Therapy Cohort Compared with Lag-Time Therapy

	Outpatient Visit			Hospitalization			Death		
	In Time/ Lag Time	OR (95% CI)	*P* Value	In Time/ Lag Time	OR (95% CI)	*P* Value	In Time/ Lag Time	OR (95% CI)	*P* Value
Total	9502/18174	0.50 (0.49–0.52)	<0001	85/196	0.54 (0.37–0.62)	<0001	104/165	0.71 (0.56–0.91)	<0001
Cohort									
2005s	81/133	0.23 (0.17–0.31)	<0001	4/3	0.71 (0.16–3.19)	0.6521	2/3	0.35 (0.06–2.12)	0.2350
2009s	7859/15386	0.50 (0.48–0.51)	<0001	59/153	0.44 (0.33–0.60)	<0001	65/117	0.64 (0.47–0.86)	0.0035
2010s	1562/2655	0.53 (0.49–0.57)	<0001	22/40	0.58 (0.35–0.98)	0.041	37/45	0.88 (0.57–1.35)	0.5492
Age									
20–29	3619/5927	0.60 (0.58–0.63)	<0001	15/35	0.47 (0.26–0.86)	0.0117	3/6	0.55 (0.14–2.18)	0.3848
30–39	2292/4865	0.48 (0.45–0.50)	<0001	6/30	0.24 (0.10–0.58)	0.0005	5/9	0.67 (0.22–2.00)	0.4689
40–49	1567/3227	0.44 (0.41–0.47)	<0001	13/23	0.62 (0.32–1.23)	0.1699	8/18	0.49 (0.21–1.13)	0.0869
50–59	1090/2153	0.45 (0.41–0.49)	<0001	13/31	0.48 (0.25–0.91)	0.0220	15/21	0.81 (0.42–1.58)	0.5414
60–69	433/962	0.36 (0.32–0.42)	<0001	8/14	0.66 (0.28–1.58)	0.3451	16/22	0.84 (0.44–1.60)	0.5959
70–79	287/676	0.34 (0.29–0.41)	<0001	9/30	0.35 (0.17–0.75)	0.0044	21/36	0.69 (0.40–1.19)	0.1786
≧80	214/364	0.48 (0.38–0.59)	<0001	21/33	0.67 (0.38–1.17)	0.1582	36/53	0.71 (0.46–1.10)	0.1260
Gender									
Men	4203/7108	0.50 (0.48–0.52)	<0001	51/104	0.48 (0.34–0.67)		66/106	0.61 (0.45–0.83)	0.0015
Women	5299/11066	0.51 (0.49–0.53)	<0001	34/92	0.47 (0.32–0.70)	0.0001	38/59	0.82 (0.54–1.23)	0.3341

CI, confidence interval; OR, odds ratio.

in hospitalization risk remained significant for most age groups. Reductions in outpatient visits and hospitalization were similar in men and women, while the reduction in mortality risk was significant for men, but not for women.

Table 3 shows in-time relative to lag-time ORs of repeat outpatient visits, hospitalization and death associated with age and sex. The risk of repeat outpatient visits, hospitalization or death increased with age. Compared with patients 20 to 29 years old, the OR of death was increased to 307 (95% CI = 154–611, $P < 0.0001$) in patients aged 80 years and above. Men were at lower risk of repeat outpatient visits (OR = 0.84, 95% CI = 0.82–0.86) but at higher risk of hospitalization (OR = 1.39, 95% CI = 1.1–1.77) or death (OR = 1.83, 95% CI = 1.41–2.36). Table 4 shows that the superior effectiveness of the in-time oseltamivir therapy relative to lag-time for all events changed slightly between 2009 and 2010, with overall ORs of 0.50 (95% CI = 0.49–0.52) and 0.54(95% CI = 0.50–0.58), respectively.

DISCUSSION

Oral oseltamivir is a well-tolerated and effective antiviral drug for influenza patients of all ages, even for those with comorbidities of respiratory diseases and/or chronic cardiac disease.[17] Population-based study on antiviral efficacy has been limited to retrospective cohort study because it is difficult to perform a randomized population trial.[14–16] Our study used insurance claims data to perform another retrospective cohort study. The results showed that oseltamivir treatment was also effective for Asian patients with influenza infection of all ages in 2005, 2009, or 2010. Previous studies emphasized in evaluating whether the oseltamivir treatment reduced lower respiratory tract complications, antibiotic use and/or hospitalization, alleviated symptoms, or reduced mortality.[8,18–21] An earlier double blind prospective trial involving 3564 flu patients concluded that the oseltamivir treatment could reduce lower respiratory tract complications, antibiotic use, and hospitalization.[8]

Studies recommended early treatment with oseltamivir for patients with influenza A (H1N1 and H5N1).[21–23] Delayed oseltamivir treatment increases the lung involvement.[24] An UK study found that in influenza patients treated with oseltamivir 75 mg within 24 hours of symptom onset, the duration of symptoms was 43 hours shorter than placebo controls.[18] A Japanese study found that pediatric patients with 2009 H1N1 infection treated within 48 hours of symptom onset with neuraminidase inhibitors, primarily oseltamivir, could reduce case fatality to 0.1%.[21] Nursing home and hospital studies on oseltamivir therapy also showed that the in-time treatment reduced the disease spread, duration of illness, level of viral shedding, and respiratory failure.[25–30]

Our study defined oseltamivir treatment within 1 week of symptom onset as the prompt in-time treatment. The in-time treatment was consistently superior to the lag-time treatment in the reduction of adverse events; there were overall 50% (OR = 0.50) reduction in repeat outpatient visits, 46% (OR = 0.54) reduction in hospitalization, and 29% (OR = 0.71) reduction in mortality within the 2-week follow-up period (Table 2). The superior effects of the in-time treatment appeared in each study year, each age group, males, and females. The stratified analysis, however, showed that the fatality reduction was significant only in 2009 and for men. We were unable to observe a significant trend for the emergency admission due to small sample size.

Studies have reported that the 2008 to 2009 influenza A (H1N1) viruses exhibited decreased susceptibility to oseltamivir.[30–32] Using influenza surveillance network laboratories study of the Taiwan Centers for Disease Control, Yang et al found that the oseltamivir-resistant influenza virus had developed in Taiwan during the pandemic outbreak.[30,32] The trend of oseltamivir resistance also appeared noticeable in our study results of 2009 and 2010. Our data showed that the outpatient visit, hospitalization, and mortality were higher in 2010, especially for the patients receiving delayed oseltamivir treatment. We

TABLE 3. Logistic Regression Analysis Estimated In-Time to Lag-Time ORs of Repeat Outpatient Visit, Hospitalization and Death, and ORs Among Age Groups and Between Men and Women

	Outpatient		Hospitalization		Death	
	OR	***P***	**OR**	***P***	**OR**	***P***
In time versus lag time	0.50 (0.49–0.52)	<0001	0.48 (0.37–0.62)	<0001	0.70 (0.54–0.89)	0.0043
Age						
20–29	1.0		1.0		1.0	
30–39	1.26 (1.22–1.31)	<0001	1.19 (0.78–1.83)	<0001	2.67 (1.16–6.17)	<0001
40–49	1.35 (1.3–1.41)	<0001	1.84 (1.20–2.82)	<0001	7.46 (3.50–15.9)	<0001
50–59	1.90 (1.81–2.00)	<0001	4.33 (2.88–6.50)	<0001	20.3 (9.76–42.1)	<0001
60–69	2.30 (2.14–2.46)	<0001	5.63 (3.41–9.31)	<0001	55.9 (27.0–115.8)	<0001
70–79	2.45 (2.25–2.67)	<0001	14.3 (9.40–21.8)	<0001	117.3 (58.0–237.2)	<0001
≧80	2.55 (2.29–2.84)	<0001	33.7 (22.8–49.7)	<0001	307.2 (154.4–611.4)	<0001
Gender						
Women	1.0		1.0		1.0	
Men	0.84 (0.82–0.86)	<0001	1.39 (1.1–1.77)	<0001	1.83 (1.41–2.36)	<0001

OR, odds ratio.

conducted a further analysis to compare all the events using the study year as a covariate. Compared with 2005, the adjusted ORs of having adverse events were 1.81 (95% CI = 1.55–2.11) in 2009 and 2.04 (95% CI = 1.74–2.38) in 2010 (data not shown). The overall in-time to lag-time treatment OR of all events, however, changed slightly from 0.50 in 2009 to 0.54 in 2010, indicating that the early oseltamivir treatment remains an effective choice for interrupting seasonal influenza. The oseltamivir-resistant virus might be slightly happening in 2010 in Taiwan's population.

This study is an example using population-based insurance claims data to evaluate the treatment progress of prompt initiation of oseltamivir therapy for reducing repeat outpatient visits, hospitalizations, and mortality in an Asian population. In addition to a large number of study population, we examined a wide range of age groups, including the elderly. Unlike clinical trials, this natural history study was able to demonstrate that an earlier antiretroviral administration reduced near half of odds for outpatient visits and hospitalization.

Our study has a number of limitations. First, the nature of retrospective study has an inherent limitation of selection bias. Patients administered with oseltamivir usually suffered from severe influenza symptoms. Thus, our study results may not be applicable to patients with mild symptoms. Second, Taiwan government provided free oseltamivir to patients only in 2005, 2009, and 2010, we therefore constrained the current study using data available for these 3 years. Nevertheless, our study results show that oseltamivir is effective and useful to relieve influenza symptoms, especially for the in-time cohort. The clinical features show that patients in the in-time cohort usually suffer from more severe symptoms at the onset of influenza than those who are in the lag-time cohort. If early oseltamivir treatment is more effective for patients with severe symptoms than those with mild symptoms, such treatment should be more significant for patients with severe symptoms. Third, some personal factors such as body mass index, lifestyle, and family medical history were not considered in our study because of lack of related information. Finally, we only identified the

TABLE 4. Logistic Regression Analysis Estimated In-Time to Lag-Time ORs of Repeat Outpatient Visit, Hospitalization and Death, and ORs Among Age Groups and Between Men and Women in 2009 and 2010

	2009		2010	
	OR	***P***	**OR**	***P***
In time versus lag time	0.50 (0.49–0.52)	<0001	0.54 (0.50–0.58)	<0001
Age				
20–29	Ref.		Ref.	
30–39	1.24 (1.19–1.29)	<0001	1.40 (1.27–1.53)	<0001
40–49	1.35 (1.29–1.41)	<0001	1.49 (1.33–1.67)	<0001
50–59	1.95 (1.85–2.06)	<0001	1.82 (1.61–2.06)	<0001
60–69	2.46 (2.27–2.67)	<0001	2.42 (2.06–2.85)	<0001
70–79	3.05 (2.76–3.38)	<0001	2.48 (2.05–3.00)	<0001
≧80	3.66 (3.21–4.16)	<0001	3.24 (2.61–4.03)	<0001
Gender				
Women	Ref.		Ref.	
Men	0.84 (0.82–0.87)	<0001	0.88 (0.82–0.95)	<0001

OR, odds ratio.

patients infected with influenza, but we did not analyze the subtype to which the influenza belonged to. Future studies can be conducted to examine the treatment effectiveness of oseltamivir on the subtypes of influenza.

CONCLUSIONS

Oseltamivir therapy was initiated with a small size trial for mainly elderly patients in 2005 in Taiwan, which resulted successful effectiveness on reducing outpatient visit, hospitalization, and mortality. Oseltamivir also exhibits superior effectiveness in reducing outpatient visit, hospitalization, and mortality when much larger sizes of patients were treated promptly in 2009 and 2010, although minor variant in drug resistance was noted from 2009 to 2010. This national data with large sample size obviously shows that oseltamivir is an effective medicine until now, especially in reducing the reoutpatient visit rates for patients of all ages.

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