Socioeconomic Factors Influencing Hospitalized Patients with Pneumonia Due to Influenza A(H1N1)pdm09 in Mexico

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Abstract

Background: In addition to clinical aspects and pathogen characteristics, people's health-related behavior and socioeconomic conditions can affect the occurrence and severity of diseases including influenza A(H1N1)pdm09.

Methodology and Principal Findings: A face-to-face interview survey was conducted in a hospital in Mexico City at the time of follow-up consultation for hospitalized patients with pneumonia due to influenza virus infection. In all, 302 subjects were enrolled and divided into two groups based on the period of hospitalization. Among them, 211 tested positive for influenza A(H1N1)pdm09 virus by real-time reverse-transcriptase-polymerase-chain-reaction during the pandemic period (Group-pdm) and 91 tested positive for influenza A virus in the post-pandemic period (Group-post). All subjects were treated with oseltamivir. Data on the demographic characteristics, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, and related clinical data were compared between subjects in Group-pdm and those in Group-post. The ability of household income to pay for utilities, food, and health care services as well as housing quality in terms of construction materials and number of rooms revealed a significant difference: Group-post had lower socioeconomic status than Group-pdm. Group-post had lower availability of information regarding H1N1 influenza than Group-pdm. These results indicate that subjects in Group-post had difficulty receiving necessary information relating to influenza and were more likely to be impoverished than those in Group-pdm. Possible factors influencing time to seeking health care were number of household rooms, having received information on the necessity of quick access to health care, and house construction materials.

Conclusions: Health-care-seeking behavior, poverty level, and the distribution of information affect the occurrence and severity of pneumonia due to H1N1 virus from a socioeconomic point of view. These socioeconomic factors may explain the different patterns of morbidity and mortality for H1N1 influenza observed among different countries and regions.

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Introduction

In March 2009, Mexico was the first country to raise the international alert about the outbreak of influenza A(H1N1)pdm09 virus infection [1]. The pandemic spread rapidly worldwide; however, the number of severe and fatal cases differed among different countries and regions [2]. In Mexico, there were large numbers of hospitalized patients with acute and severe illness, and fatalities occurred [1,2,3,4,5]. Many patients with influenza-like symptoms, including pneumonia, presented to the National Institute of Respiratory Disease (INER), Mexico City, Mexico; a number of these required hospitalization owing to the severity of the illness, and there were fatalities, especially at the early stage of the pandemic [1]. After the announcement of the post-pandemic period for influenza A(H1N1)pdm09 by the World Health Organization (WHO) [6], effective management of the influenza pandemic continued to be a major concern. Clinical preparedness for A(H1N1)pdm09 was based on an understanding of the pathogenic characteristics of the virus and host immune-response patterns as well as the ability to undertake clinical interventions and ordinary individuals' knowledge about prevention; all of these factors were thought to have been at a developed stage in Mexico following the experiences of the 2009 influenza pandemic. However, a similar number of hospitalized patients with influenza-associated pneumonia presented again to the INER in the post-pandemic period [7].

Various factors affecting occurrence of pneumonia, disease severity, and mortality associated with A(H1N1)pdm09H1N1 have been reported from a clinical viewpoint [8,9,10,11]. Other

underlying conditions, including such environmental and socio-economic factors as education and poverty, are also thought to affect the disease morbidity and mortality [12,13]. However, only limited data are available regarding the influence of socioeconomic factors on the occurrence of pneumonia related to influenza virus infection. Previously, we reported that the number of days between symptom onset and oseltamivir treatment affects the occurrence and severity of pneumonia due to H1N1 influenza [14]. Delayed treatment is associated with socioeconomic difficulties of INER patients [14]. A study in Canada also showed that delayed antiviral treatment is independently associated with disease severity [15]. We hypothesize that some risk factors affecting the continued occurrence of pneumonia in the post-pandemic period in Mexico, including delay in seeking healthcare, need to be addressed from the socioeconomic rather than clinical point of view. These factors may explain the different mortality and morbidity patterns for A(H1N1)pdm09 in different countries and regions.

The aim of the present study was to assess how socioeconomic and living conditions relate to the disease severity of H1N1 influenza, including pneumonia, in Mexico.

Materials and Methods

Study design

The survey was conducted at the INER, Mexico City between December 2010 and April 2011, and it included follow-up consultation with subjects or their relatives using structured questionnaires administered by physicians or trained medical staff. The subjects were former patients hospitalized in the INER for pneumonia due to A(H1N1)pdm09 who tested positive by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) during the pandemic period; patients hospitalized for pneumonia who tested positive for influenza A virus during the post-pandemic period served as a comparison group. Patients with pneumonia caused by primary bacterial infection were excluded. All subjects were treated with oseltamivir. The pandemic period was defined as April 2009 to July 2010, and the post-pandemic period was defined as August 2010 to March 2011, in accordance with the declaration of the post-pandemic period by the WHO [9]. No subjects were hospitalized in both the pandemic and post-pandemic periods.

The questionnaire was designed to collect data on the demographic characteristics of subjects, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, as well as related clinical data. Socioeconomic status was classified in terms of daily income while living environment was defined in terms of numerous factors associated to living conditions, including area in which subjects lived (i.e., location), house size and construction material, among other factors. All questions were either closed-ended or multiple choice. Each variable was compared between subjects hospitalized in the pandemic period (Group-pdm) and those hospitalized in the post-pandemic period (Group-post). In addition, factors affecting access to health care were evaluated. Socioeconomic level was classified based on daily income and on the ability of household income to pay for utilities, food, and medical services according to the Social Gap Index by the CONEVAL (Consejo Nacional de Evaluación de la Política de Desarrollo Social) [16]. Location was defined by the accessibility to public service which was also evaluated according to the Social Gap Index.

All subjects provided written informed consent. Ethical approval was provided by the Institutional Review Board of the National Institute of Respiratory Diseases, Mexico City and the National Center for Global Health and Medicine, Tokyo. The investigators maintained the datasets in password-protected systems and have preserved the anonymity of the subjects when presenting data.

Statistical Analysis

Data from the surveys were double-entered and analyzed using SPSS ver. 19 (IBM, Armonk, NY, USA). For categorical variables, frequencies were compared using the chi-square test and Fisher's exact test. For determination of independent factors for the time to seeking healthcare, multivariate regression analysis was conducted using a stepwise selection method included all variables in baseline characteristics, socioeconomic status, living environment, and information relating to A(H1N1)pdm09, and related clinical data, if $p < 0.1$ in univariate analysis. For all analyses, significance levels were two-tailed, and p value of <0.05 was considered significant.

Results

General and health-related backgrounds for study subjects

In all, 302 subjects who were hospitalized with pneumonia between April 2009 and March 2011 and received follow-up consultation during the study period agreed to participate in the present survey. Among them, 211 (69.9%) were hospitalized during the pandemic period (Group-pdm) and 91 (30.3%) in the post-pandemic period (Group-post). The general backgrounds of subjects are listed (Table 1). The median ages of subjects in Group-pdm and Group-post were 38.5 (range, 0–90) years and 42.0 (range, 2–91) years, respectively. There was a higher percentage of younger subjects in Group-pdm than in Group-post ($p = 0.001$). There was no significant sex difference between the groups ($p = 0.354$). Approximately 17% of the subjects had received no education, and there was no significant difference in education level between the groups ($p = 0.356$). Although unemployment was higher in Group-post (18.7%) than in Group-pdm (8.6%), the occupations were not significantly different between the groups ($p = 0.437$). The socioeconomic level of 70.5% of all subjects was low, whereas 29.5% were of middle socioeconomic level ($p = 0.332$).

The health-related background details of subjects are presented in Table 1. The rate of seasonal influenza vaccination was approximately 20% in both groups in 2010; however, the vaccinated populations in 2009 and 2011 were smaller than in 2010. There were significantly more smokers in Group-post (23.1%) than in Group-pdm (8.1%) ($p = 0.002$). Medication for chronic respiratory illness was being taken by 2.8% of Group-pdm subjects and 44.0% of Group-post subjects ($p<0.001$). The median number of days to initiation of oseltamivir administration from symptom onset for all subjects was 6 days (range, 0–35) and there was no significant difference between the groups ($p = 0.379$).

Economic factors

The detailed economic situation of the subjects was defined by the Social Gap Index of COVEVAL (Table 2). The ability of household income to pay for all utility services (light, gas, water, sewerage, and telephone) or some (two or three of the five) was significantly lower in Group-post than in Group-pdm ($p<0.001$). The ability of household income to pay for all foods (meat, egg, milk, cereals, vegetables) or some foods (two or three of the five) was 59.7% and 40.3%, respectively, in Group-pdm vs. 27.8% and 56.7%, respectively, in Group-post ($p<0.001$); 15.6% of the subjects in Group-post stated that could not pay for any food from their income. The ability of household income to pay for all health

Table 1. General and health-related backgrounds of study subjects.

	Pandemic period*	Post-pandemic period*	Total	p value
	N = 211 (69.9%)	N = 91 (30.3%)	N = 302 (100.0%)	
Gender				
Male-no. (% of group)	128 (60.7)	50 (54.9%)	178 (58.9%)	0.354
Age – median (range)	38.5 (0–90)	42.0 (2–91)	39.0 (0–91)	0.003
Age group – no. (% of group)				0.001
<18	45 (21.4)	4 (4.4)	49 (16.3)	
18-<50	108 (51.2)	52 (57.1)	160 (53.0)	
50-<65	43 (20.4)	22 (24.2)	65 (21.5)	
≥65	15 (7.1)	13 (14.3)	28 (9.3)	
Education background – no. (% of group)				0.356
None	34 (16.4)	17 (17.9)	51 (16.9)	
Primary school	57 (27.5)	25 (26.3)	82 (27.2)	
Secondary school	49 (23.7)	16 (16.8)	65 (21.5)	
High school	33 (15.9)	19 (20.0)	52 (17.2)	
University	30 (14.5)	12 (12.6)	42 (13.9)	
Graduate school	2 (1.0)	3 (3.2)	5 (1.7)	
Technical school	2 (1.0)	3 (3.2)	5 (1.7)	
Occupation – no. (% of group)				0.437
Unemployed	18 (8.6)	17 (18.7)	35 (11.7)	
Retired	1 (0.5)	2 (2.2)	3 (1.0)	
Student	28 (13.4)	3 (3.3)	31 (10.3)	
Housewife	53 (25.4)	30 (33.0)	83 (27.7)	
Governmental employee	4 (1.9)	3 (3.3)	7 (2.3)	
Employee by private company	30 (14.4)	15 (16.5)	45 (15.0)	
Commercial	33 (15.8)	5 (5.5)	38 (12.7)	
Self-employed (small business)	28 (13.4)	3 (3.3)	31 (10.3)	
Socioeconomic level†				0.332
Low	144 (72.4)	69 (67.0)	213 (70.5)	
Middle	55 (27.6)	34 (33.0)	89 (29.5)	
High	0 (0.0)	0 (0.0)	0 (0.0)	
Heath-related background				
Vaccination (seasonal influenza)				0.203
Vaccinated in 2009	4 (1.9)	6 (6.6)	10 (3.3)	
Vaccinated in 2010	42 (19.9)	20 (22.0)	62 (20.5)	
Vaccinated in 2011	8 (3.8)	3 (3.5)	11 (3.6)	
Smoking				0.002
smoker	18 (8.5)	21 (23.1)	39 (12.9)	
ex-smoker	19 (9.0)	8 (8.8)	27 (8.9)	
Chronic respiratory illness on medication	6 (2.8)	40 (44.0)	46 (15.2)	0.000
Days from symptom onset to initiation of treatment – median (range)‡	6.0 (0–35)	5.0 (0–29)	6.0 (0–35)	0.379

*Pandemic period, between April 2009 and July 2010; Post-pandemic period, between August 2010 and the end of survey period.
†Socioeconomic level evaluated by ability to pay for utilities, food, and medical service: low income, cannot cover electricity, water, telephone, house rent, foods, any medical service; middle income, can cover a part of electricity, water, telephone, house rent, and foods, but not any medical service; high income, can cover utility and adequate goods, and medical services.
‡Number of days from symptom onset to initiation of oseltamivir administration.
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care services (consultation, hospitalization, and medication) or some of them (consultation and hospitalization) were 28.8% and 67.6%, respectively, in Group-pdm vs. 17.8% and 38.9%, respectively, in Group-post ($p<0.001$); 82.8% of subjects were uninsured.

Table 2. Detailed economic status of study subjects.

	Pandemic period*i	Post-pandemic period*	Total	p value
	N = 211 (69.9%)	N = 91 (30.3%)	N = 302 (100.0%)	
Income ability to pay for utility services†				0.000
All services	76 (36.0)	16 (17.6)	92 (30.5)	
2–3 of all	133 (63.0)	41 (45.1)	174 (57.6)	
None	2 (0.9)	34 (37.4)	36 (11.9)	
Income ability to pay for food‡				0.000
All necessaries	126 (59.7)	25 (27.8)	151 (50.2)	
2–3 of all	85 (40.3)	51 (56.7)	136 (45.2)	
None	0 (0.0)	14 (15.6)	14 (4.7)	
Income ability to pay for Health care service				0.000
Consultation, hospitalization, medication	60 (28.6)	16 (17.8)	76 (25.3)	
Consultation, hospitalization	142 (67.6)	35 (38.9)	177 (59.0)	
None	8 (3.8)	39 (43.3)	47 (15.7)	
Health insurance				0.144
None	179 (84.8)	71 (78.0)	250 (82.8)	
Government insurance§	17 (8.1)	8 (8.8)	25 (8.3)	
Private insurance	1 (0.5)	0 (0.0)	1 (0.3)	
Others	14 (6.6)	12 (13.2)	26 (8.6)	

*Pandemic period, between April 2009 and July 2010; Post-pandemic period, between August 2010 and the end of survey period.
†Income can pay for expense of utilities; light, gas, water, sewerage, telephone.
‡Income can pay for expense of food; meat, egg, milk, cereals, vegetable.
§Governmental insurance included workers in private organizations.
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Life environment

Most of the subjects in Group-pdm and Group-post lived in an area that provided all public services ($p = 0.144$), and there was no difference between the groups. In terms of housing status (Table 3), 39.8% and 30.8% of subjects in Group-pdm and Group-post lived for free in borrowed accommodation, whereas 18.5% and 34.1%, respectively, lived in rental accommodation; there was a significant difference in housing status between the groups ($p = 0.011$). Although most Group-pdm subjects lived in concrete houses or a combination of concrete and tinplate houses, more subjects in Group-post lived only in tinplate houses, and there was a significant difference in housing quality between the groups ($p<0.001$). The number of rooms and individuals living in a house were significantly different between the groups ($p = 0.003$ and $p<0.001$, respectively). The median number of individuals per room in each household was 2.5 (range, 0.29–8.0) in Group-pdm and 3.0 (range, 0.67–9.0) in Group-post, and there was a significant difference between the groups ($p<0.001$).

Information relating to H1N1 virus infection

The most common source of information about influenza A(H1N1)pdm09 was television in both groups ($p = 0.706$) (Table 4). Although subjects in Group-pdm were more likely than those in Group-post to be informed through radio (55.5% vs. 25.3%, $p<0.001$), there was no significant difference in the use of other sources of information between the groups.

More Group-pdm subjects than Group-post subjects received clear information about methods of prevention of influenza A(H1N1)pdm09 (77.3% vs. 29.7%, respectively, $p<0.001$) as well as information regarding the necessity for early access to health care (94.3% vs. 60.4%, respectively, $p<0.001$).

Delay in seeking health care from symptom onset in hospitalized patients with pneumonia

In the multivariate regression analysis, the number of household rooms, information regarding the necessity for quick access to health care, and housing construction materials were independent factors that tended to be associated with the number of days from symptom onset to the initiation of antiviral treatment (Table 5). Since the INER administered antiviral treatment soon after hospital admission to hospitalized patients with pneumonia, the number of days to initiation of antiviral treatment was practically the same as the number of days from symptom onset to first access to formal health care.

Discussion

Low awareness of the importance of early access to healthcare and difficulty separating oneself from other individuals in a household owing to poverty are possible reasons for hospitalized pneumonia due to influenza virus infection in the post pandemic period.

INER is a tertiary medical organization for the care of patients with respiratory illness, and it provides medical services mainly to uninsured individuals in the metropolitan area of Mexico City and neighboring states. Most patients who visit the INER have a similar low socioeconomic level, demographic characteristics, and educational background [17], including the subjects in the present

Table 3. Life environmental qualities of study subjects.

	Pandemic period*	Post-pandemic period*	Total	p value
	N = 211 (69.9%)	N = 91 (30.3%)	N = 302 (100.0%)	
Location†				0.144
All public services	187 (88.6)	75 (82.4)	262 (86.8)	
Partial public services	24 (11.4)	16 (17.6)	40 (13.2)	
Housing				0.011
Borrow without any payment	84 (39.8)	28 (30.8)	112 (37.1)	
Rent	39 (18.5)	31 (34.1)	70 (23.2)	
Pay for credit	16 (7.6)	2 (2.2)	18 (6.0)	
Own	72 (34.1)	30 (33.0)	102 (33.8)	
House construction material				<0.001
Concrete	179 (84.8)	70 (76.9)	249 (82.5)	
Tinplate	3 (1.4)	12 (13.2)	15 (5.0)	
Concrete and tinplate	29 (13.7)	9 (9.9)	38 (12.6)	
Number of rooms in a house				0.003
≤2	85 (40.3)	64 (70.3)	149 (49.3)	
3–5	121 (57.3)	26 (28.6)	147 (48.7)	
≥6	5 (2.4)	1 (1.1)	6 (2.0)	
Number of individuals in a house				<0.001
≤2	13 (6.2)	24 (26.4)	37 (12.3)	
3–5	167 (79.5)	57 (62.6)	224 (74.4)	
≥6	30 (14.3)	10 (11.0)	40 (13.3)	
Number of individuals per a room, mean (range)	2.5 (0.29–8.0)	3.0 (0.67–9.0)	2.5 (0.29–9.0)	<0.001

*Pandemic period, between April 2009 and July 2010; Post-pandemic period, between August 2010 and the end of survey period.
†Location was defined by the accessibility of public service which is also followed by the Social Gap Index.
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study (Table 1). A detailed evaluation of socioeconomic similar subjects using the Social Gap Index of CONEVAL [16] revealed

Table 4. Availability of information related to influenza A(H1N1)pdm09.

	Pandemic period*	Post-pandemic period*	Total	p value
	N = 211 (69.9%)	N = 91 (30.3%)	N = 302 (100.0%)	
Information resources				
Newspaper	34 (16.1)	13 (14.3)	47 (15.6)	0.688
Television	170 (80.6)	75 (82.4)	245 (81.1)	0.706
Radio	116 (55.5)	23 (25.3)	139 (46.3)	0.000
Internet	4 (1.9)	3 (3.3)	7 (2.3)	0.355
Family and friends	22 (10.4)	15 (16.5)	37 (12.3)	0.141
Healthcare workers in Hospital	23 (10.9)	3 (3.3)	26 (8.6)	0.031
No information	1 (0.5)	3 (3.3)	4 (1.3)	0.083
Received clear information how to prevent influenza?	163 (77.3)	27 (29.7)	190 (62.9)	0.000
Received the information for the necessity of quick access to healthcare.	199 (94.3)	55 (60.4)	254 (84.1)	0.000

*Pandemic period, between April 2009 and July 2010; Post-pandemic period, between August 2010 and the end of survey period.
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Table 5. Factors relating to delayed seeking of health care, using multivariate analysis.

	Coefficient	Standard error	t value	p value	95% confidence interval
Constant	−10.246	4.351	−2.355	0.022	−18.985–−1.508
Number of rooms in house	3.798	0.895	4.242	0.000	2.000–5.597
Received information about necessity of quick access to health care during pandemic period	4.741	1.986	2.387	0.021	0.751–8.730
House construction material*	3.056	1.473	2.075	0.043	0.097–6.015

*House constructed of concrete, tinplate, and combination of concrete and tinplate.
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that <1% in Group-pdm were unable to pay for either utility services or food; there was a greater number of such subjects in Group-post (Table 2). Moreover, approximately half of the subjects in Group-post were unable to pay for health-care services. In contrast to Group-pdm subjects, those in Group-post lived in houses constructed of tinplate with fewer rooms, and there was also a greater number of individuals sharing the same house (Table 3). These results reflect the situation of many poor people in Mexico City, who live together with relatives and friends and help one another in their daily lives, including payments for utilities and food [19]. The subjects in Group-post were more likely to be impoverished than those in Group-pdm and showed a greater tendency to engage in mutual support. Economic difficulties and the inability to pay for treatment create problems in accessing formal health care in the early stage of any illness, even if the cause is acute viral infection; these factors can lead to the delayed initiation of appropriate treatment. For people without health-care insurance and who are paid on a daily basis, it is especially hard to stop work and seek medical assistance, even for a day. As a result, by the time they present to a hospital, their disease has progressed and may have become severe. This was the situation for patients in both Group-pdm and Group-post; however, those in Group-post faced greater poverty. There was a greater number of patients facing economic difficulties in Group-post than in Group-pdm, which indicates that subjects in the former group may have experienced more problems in accessing early health care. We previously showed that patients with severe pneumonia had a lower socioeconomic level and delayed initiation of oseltamivir treatment [14]. Patients in Group-post lived in houses with fewer rooms, but they also lived together with a greater number of other individuals (Table 3). This reflects not only the socioeconomic level of the subjects, but also an increased risk for human-to-human transmission of the influenza virus.

In Mexico, rural poverty is concentrated in southern areas of the country [19,20]. Especially during the early stage of the influenza outbreak in 2009, there was a high rate of infection in populations in areas of rural poverty in the south including Mexico City [21]. However, Mexico City is not a single metropolitan area but a growing megalopolis. The city incorporates surrounding areas of poverty, and low- and middle-income communities live in close proximity in the same area. Most of the subjects in the present study were impoverished; however, >80% of them were located in areas with access to all public services, and there was no significant difference between the subjects in Group-pdm and Group-post (Table 3). This is typical of the unique living environment in Mexico City, and it reflects the traditional Mexican custom of social support, whereby high- and middle-income individuals help those with low or no income [19]. Impoverished people in Mexico City depend for their daily existence on those with high and middle incomes; therefore, they need to live close to high- and middle-income areas. As a result, there was no significant difference in residential location between the subjects in Group-pdm and Group-post (Table 3).

Seasonal influenza vaccination in Mexico is limited to the young and elderly [22]. Although a previous study reported that vaccination status was independently associated with H1N1 influenza [23], there was no significant difference between the groups in the present study (Table 1). Although smoking is also associated with H1N1 influenza [2,18], there were significantly more smokers in Group-post than in Group-pdm ($p = 0.002$), which may reflect the fact that there were more elderly patients in Group-post ($p = 0.001$). In terms of comorbid conditions, more patients in Group-post had chronic respiratory illness than did those in Group-pdm ($p < 0.001$). These results indicate that H1N1 influenza is an emerging infectious disease that could infect individuals beyond the population without underlying respiratory illness. One year after the influenza outbreak, after some of the population had gained immunity [24,25], the elderly population with underlying respiratory illness and who were smokers were more likely to be susceptible to influenza virus infection than the younger population without underlying respiratory illness.

The time from onset of symptoms to initiation of oseltamivir treatment is a key factor in reducing severe respiratory conditions due to H1N1 influenza [14,15]. The time to initiation of oseltamivir treatment depended on health-care-seeking behavior. After the first manifestation of the outbreak in Mexico, the mass media drew attention to the disease and created a sense of fear in the population [18]. However, among impoverished individuals and those with less education, it may be difficult to obtain information from media sources. Although television was a major source of information for the patients in our study (Table 4), more patients in Group-post than in Group-pdm did not receive information about methods of prevention of H1N1 influenza infection and the necessity for quick access to health care ($p<0.001$). This indicates the importance of the method of information distribution and education for enhancing the social response to an influenza pandemic. We also evaluated the factors affecting the time from symptom onset to initiation of oseltamivir treatment (Table 5). The number of rooms in the household, receiving information about the necessity of quick access to health care, and house construction materials were evaluated as independent factors that possibly influenced health-care-seeking behavior. Poverty is associated with difficult housing conditions including the number of rooms and house construction materials. It also associated with lower access to information from media resources that could motivate people to seek early access to health care owing to a lack of utility services in the household. In addition, fewer rooms in a household was associated with

increased risk of human-to-human infection. This indicates that poverty strongly influences health-care-seeking behavior and suggests the importance of distribution of information and educational resources.

The present study was limited to a population that was mostly uninsured and facing socioeconomic difficulties in Mexico City. Although there is a large gap between poverty and wealth in Mexico, the present study did not evaluate the range of socioeconomic levels in the population. Patients in Group-pdm had H1N1 influenza confirmed by RT-PCR, but the same test was not performed in patients in Group-post for budgetary reasons in the INER. Therefore, Group-post may have included patients with pneumonia not caused by influenza A(H1N1)pdm09 virus, but by some other type of influenza A virus. Further study, including an investigation of different socioeconomic populations, is needed to determine the impact of socioeconomics on the severity of disease due to influenza infection.

Although many factors affect disease occurrence and severity (including pneumonia), health-care-seeking behavior, poverty, and distribution of information are important factors from a socioeconomic point of view. These factors may explain the different patterns of morbidity and mortality for influenza A(H1N1)pdm09 in different countries and regions.

Author Contributions

Conceived and designed the experiments: TM ALHI KK. Performed the experiments: ALHI MEVM TM KK JT SI ELMV LAR. Analyzed the data: TM ALHI KK. Wrote the paper: TM KK.

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Systemic Corticosteroids and Early Administration of Antiviral Agents for Pneumonia with Acute Wheezing due to Influenza A(H1N1)pdm09 in Japan

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Abstract

Background: Pneumonia patients with wheezing due to influenza A(H1N1)pdm09 were frequently treated with systemic corticosteroids in Japan although systemic corticosteroid for critically ill patients with pneumonia caused by influenza A(H1N1)pdm09 has been controversial. Applicability of systemic corticosteroid treatment needs to be evaluated.

Methods/Principal Findings: We retrospectively reviewed 89 subjects who were diagnosed with influenza A(H1N1)pdm09 and admitted to a national hospital, Tokyo during the pandemic period. The median age of subjects (45 males) was 8 years (range, 0–71). All subjects were treated with antiviral agents and the median time from symptom onset to initiation of antiviral agents was 2 days (range, 0–7). Subjects were classified into four groups: upper respiratory tract infection, wheezing illness, pneumonia with wheezing, and pneumonia without wheezing. The characteristics of each group was evaluated. A history of asthma was found more frequently in the wheezing illness (55.6%) and pneumonia with wheezing (43.3%) groups than in the other two groups ($p=0.017$). Corticosteroid treatment was assessed among subjects with pneumonia. Oxygen saturation was lower in subjects receiving corticosteroids (steroid group) than in subjects not receiving corticosteroids (no-steroid group) ($p<0.001$). The steroid group required greater oxygen supply than the no-steroid group ($p<0.001$). No significant difference was found by the Kaplan-Meier method between the steroid and the no-steroid groups in hours to fever alleviation from the initiation of antiviral agents and hospitalization days. In logistic regression analysis, wheezing, pneumonia and oxygen saturation were independent factors associated with using systemic corticosteroids.

Conclusion: Patients with wheezing and a history of asthma were frequently found in the study subjects. Systemic corticosteroids together with early administration of antiviral agents to pneumonia with wheezing and possibly without wheezing did not result in negative clinical outcomes and may prevent progression to severe pneumonia in this study population.

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Introduction

Although systemic corticosteroid treatment for severe pneumonia due to influenza A(H1N1)pdm09 has been controversial [1,2,3], systemic corticosteroid treatment in pneumonia patients especially presenting with acute wheezing induced by influenza A(H1N1)pdm09 was frequently administered at the early stage of their illness in hospitals in Japan during pandemic period. Wheezing is the end result of a narrowing of the intrathoracic airways and a limitation of expiratory air flow and is caused by many illnesses. Asthma and bronchiolitis were the main illnesses which caused wheezing in influenza A(H1N1)pdm09 virus infection [4,5,6,7,8]. Acute exacerbation of asthma is usually diagnosed in patients with wheezing and a history of asthma. It is treated with anti-asthma agents as well as systematic corticosteroids depending on the disease severity following the asthma treatment guidelines [9,10,11]. On the other hand, a previous study in preschool children with acute virus-induced wheezing indicated that systemic corticosteroid treatment was not superior to placebo [12]. Also, a study in infants with bronchiolitis concluded that treatment with systemic corticosteroid did not significantly affect hospitalization [13]. It has been physicians' questions whether pneumonia patients presenting with wheezing need to be treated with systemic corticosteroid during the pandemic period.

The aim of the present study was to evaluate if systemic corticosteroid treatment is suitable for hospitalized pneumonia patients with acute wheezing caused by influenza A(H1N1)pdm09.

Materials and Methods

Study design

We retrospectively reviewed the clinical data, chest radiologic and laboratory findings of all hospitalized patients diagnosed with

pandemic influenza A(H1N1)pdm09, admitted between August 2009 and March 2010 to the National Center for Global Health and Medicine (NCGM), which is a tertiary care hospital in Tokyo, Japan. Influenza A(H1N1)pdm09 infection was diagnosed according to case definitions developed by the World Health Organization [14]. Respiratory tract specimens of patients were either tested positive for the influenza A(H1N1)pdm09 virus by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or tested positive for influenza A virus by ImunoAce Flu® (TAUNS Laboratories, Inc.) or Espline® (Fujirebio Inc.), rapid diagnosis tests using an immunochromatography assay, which are approved by the Ministry of Health, Welfare, and Labour, Japan. Among all hospitalized patients, subjects who presented with respiratory disorders were eligible as study subjects and classified into four groups based on their respiratory disorders: upper respiratory tract infection, wheezing illness, pneumonia with wheezing, and pneumonia without wheezing (Figure 1). The four groups were compared and evaluated in terms of the relationships among clinical conditions, clinical time course, and treatments. The clinical effects for systemic corticosteroids treatment were evaluated among the subjects with pneumonia. Also, clinical factors which leaded to prescribe systemic corticosteroids were assessed among the study subjects. Systemic corticosteroid was administered based on the treatment for acute exacerbation of asthma in the asthma guidelines [9,10,11]. Wheezing was defined as a continuous high pitched sound emitting from the chest during expiration on auscultation. Pneumonia was diagnosed on the basis of infiltrative shadows on chest radiograph.

Statistical analysis

Subjects' background data and clinical laboratory values were summarized and compared among groups of respiratory disorders as well as between those who did (steroid group) and did not (no-steroid group) receive systemic corticosteroid treatment. The Mann-Whitney test and Kruskal-Wallis test were used for continuous variables, and the Chi-square test and Fisher's exact test were used for categorical variables. Survival curves on the numbers of hours to fever alleviation from initiation of administration of antiviral agents and the duration of hospitalization in the steroid and the no-steroid groups were analyzed by the Kaplan-Meier method and comparisons were made using the log-rank test. For the evaluation of independent factors for using systemic corticosteroid treatment, a step-wise selection method was used to select significant factors if $p<0.1$ in the univariate analysis for a logistic regression analysis. Data analyses were conducted using SPSS statistics ver.19 (IBM, Armonk, NY, USA). For all analyses, significance levels were two tailed, and a p value of <0.05 was considered significant.

Ethics statement

The study was approved by the Institutional Review Board of the NCGM. Informed consent was waived by the Board for this retrospective study, with the study notification to public being made by posters. Investigators kept the datasets in password-protected systems and presented data with the anonymity of study patients retained.

Results

Characteristics of the study subjects

During the study period, a total 104 patients were diagnosed with influenza A(H1N1)pdm09 and admitted to the NCGM. Among them, 89 (85.6%) patients who presented with respiratory disorders were eligible as study subjects (Figure 1). Some subjects were admitted with reasons other than respiratory disorders including encephalopathy, dehydration, and abdominal symptoms due to influenza infection.

The number of subjects in each category of respiratory disorders was as follows: upper respiratory tract infection (n = 22, 24.7%); wheezing illness (n = 9, 10.1%); pneumonia with wheezing (n = 30, 33.7%); and pneumonia without wheezing (n = 28, 31.5%). Of all 89 subjects, the number of subjects with pneumonia was 58 (65.2%).

The characteristics of subjects according to respiratory disorders are shown in Table 1. The median age of study subjects (45 male) was 8 years (range, 0–71), and 80 subjects (89.9%) were aged less than 15 years. More subjects with wheezing illness (55.6%) or pneumonia with wheezing (43.3%) had a history of asthma than did those with upper respiratory tract infection (13.6%) or pneumonia without wheezing (17.9%), and there were significant differences among the groups ($p = 0.017$). The median oxygen saturation (SpO_2) in room air on admission in subjects with wheezing illness (91.0%) or pneumonia with wheezing (90.0%) were lower than those in subjects with upper respiratory tract infection (96.5%) or pneumonia without wheezing (93.0%), and there were significant differences among the groups ($p<0.001$). Bacterial co-infection was detected in throat swabs and/or sputum in 44.9% of subjects, but there was no significant difference among the groups. In terms of laboratory findings, including total serum Immunoglobulin E level, there were no significant differences among the groups.

Treatment and clinical time course of study subjects

The treatments and clinical time courses of study subjects in each classified group of respiratory disorders during hospitalization are shown in Table 2.

All subjects were treated with antiviral agents, either oseltamivir or zanamivir. In some subjects antiviral medication was switched from oseltamivir to zanamivir or vice versa. The regular dose of oseltamivir was 150 mg/day for 5 days in adults, and 4 mg/kg/day for 5 days in pediatric patients. The regular dose of zanamivir was 20 mg/day for 5 days. The median number of days from symptom onset to initiation of administration of antiviral agents was 1.9 (range, 1–7), and the length to antiviral treatment from the symptom onset in the pneumonia with wheezing group tended to be longer (2.4 days; range, 1–5) ($p = 0.054$).

Systemic corticosteroid was used in 93.3% of pneumonia with wheezing subjects, 77.8% of wheezing illness subjects, and 64.3% of pneumonia without wheezing subjects ($p<0.001$). The dosage of corticosteroids was equivalent to methylprednisolone 1.0–1.5 mg/body weight (kg)/time, 2–4 times/day, in subjects under 15 years of age, and 40–80 mg/time, 2–4 times/day in those over 15 years of age. The median number of days from symptom onset to initiation of administration of systemic corticosteroids was 2.1 (range, 1–6), The median duration of systemic corticosteroid treatment was 5.2 days (range, 2–9).

Treatment with anti-asthmatic agents other than corticosteroids were included in drug regimens for asthmatic episodes, cough and sputum using at least one of the following: short-acting β_2-agonist, long-acting β_2-agonist, inhaled isoproterenol, inhaled disodium cromoglycate, aminophylline, and leukotriene receptor antagonist. All subjects in wheezing illness and pneumonia with wheezing groups received anti-asthma treatments; also, 27.3% of those with respiratory tract infections and 75.0% of those with pneumonia without wheezing had at least one administration with anti-asthma agent ($p<0.001$).

Oxygen was administered using a nasal cannula or face mask to 56.2% of subjects with respiratory disorders, but no subjects required mechanical ventilation.

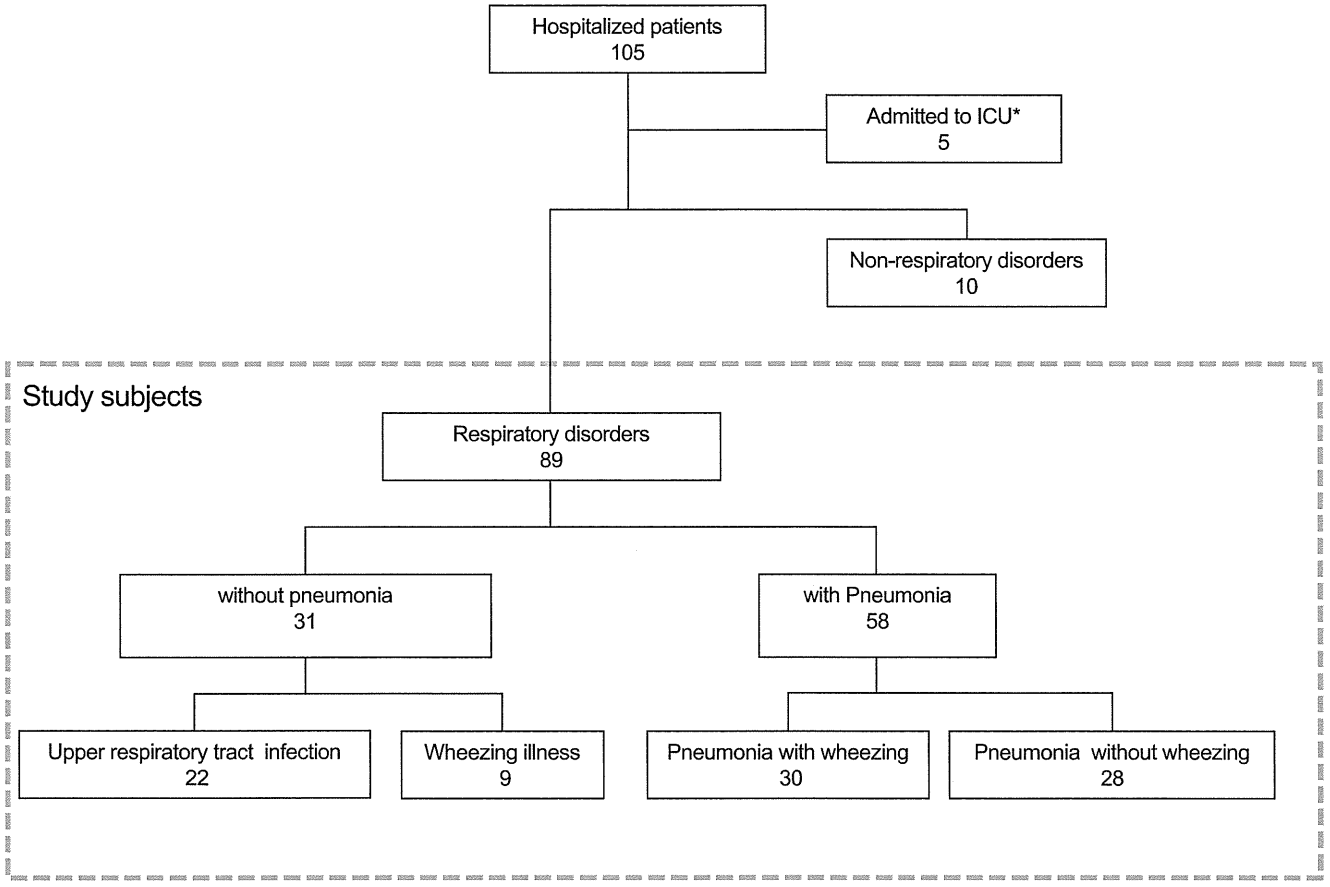

Figure 1. Study population. A total of 104 patients were diagnosed with pandemic influenza A(H1N1)pdm09. Five patients (one of whom died) were admitted to the ICU and were excluded from the study. The remaining 99 patients were the study subjects. Among them, 89 subjects presented with respiratory disorders and 10 presented with symptoms other than respiratory disorders, including encephalopathy. The subjects with respiratory disorders were classified into the following four groups: upper respiratory tract infection (n = 22), wheezing illness (n = 9), pneumonia with wheezing (n = 30), and pneumonia without wheezing (n = 28). The total number of subjects with pneumonia was 58.
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The time to fever alleviation from the initiation of administration of antiviral agents was not significantly different among the groups ($p = 0.967$). There was a longer duration of hospitalization in the pneumonia groups with and without wheezing compared with the other two groups, and there was significant difference among the groups ($p<0.001$).

Evaluation of systemic corticosteroid treatment among subjects with pneumonia

Systemic corticosteroid treatment was evaluated in subjects with pneumonia (n = 58) and compared between subjects in the steroid group and in the no-steroid group (Table 3).

Wheezing was presented 58.7% in the steroid group and there was a significant difference between the groups ($p = 0.002$). SpO_2 in the steroid group was lower than that in the no-steroid group (SpO2, 90.0% vs. 95.6, respectively; $p<0.001$) and the steroid group required more oxygen supply than the no-steroid group (97.8% vs. 8.3%, respectively; $p<0.001$). Anti-asthma treatment was applied to 97.8% of the steroid group and 50.0% of the no-steroid group ($p<0.001$). Although bacterial co-infection was found in 52.2% of the steroid group and 25.0% of the no-steroid group at the time of admission ($p = 0.093$), antibiotics were administered to both the steroid and the no-steroid groups (89.1% vs. 50.0%, respectively; $p = 0.006$). There were no significant differences in terms of time to fever alleviation (<37°C) after administration of antiviral agents and in the duration of hospitalization between the groups ($p = 0.611$ and 0.599, respectively).

Clinical time course were assessed by the Kaplan-Meier method on time to fever alleviation from the initiation of administration of antiviral agents and duration of hospitalization in subjects with pneumonia (n = 58) and compared between the steroid and the no-steroid groups using the log-rank test (Figure 2). There were no significant differences between the groups in both time to fever alleviation ($p = 0.835$) and the duration of hospitalization ($p = 0.626$).

Clinical factors for using systemic corticosteroids treatment among the study subjects

A multiple logistic regression analysis using baseline factors was conducted for subjects with respiratory disorders (n = 89). Wheezing, pneumonia and SpO_2 on admission were independent clinical factors associated with using systemic corticosteroids treatment (Table 4).

Discussion

Our evaluation of hospitalized patients with pneumonia caused by influenza A(H1N1)pdm09, who were mostly young and

Table 1. Background and clinical characteristics of study subjects.

	Upper respiratory tract infection	Wheezing* illness	Pneumonia† with wheezing	Pneumonia without wheezing	Total	P value
Number of patients (%)	22 (24.7)	9 (10.1)	30 (33.7)	28 (31.5)	89 (100.0)	0.007
Gender, male (%)	10 (45.5)	9 (100.0)	17 (56.7)	9 (32.1)	45 (50.6)	0.004
Age-yr.						0.143
<15	18 (81.8)	8 (88.9)	30 (100.0)	24 (85.7)	80 (89.9)	
≥15	4 (18.2)	1 (11.1)	0 (0.0)	4 (14.3)	9 (10.1)	
Vaccination						
Seasonal influenza vaccine of 2009–2011	3 (13.6)	2 (22.2)	7 (23.3)	5 (17.9)	17 (19.1)	0.956
Influenza A(H1N1) pdm09 vaccine	0 (0.0)	5 (27.8)	3 (16.7)	2 (33.3)	10 (18.5)	0.145
Comorbidity						
Asthma‡	3 (13.6)	5 (55.6)	13 (43.3)	5 (17.9)	26 (29.2)	0.017
Others§	1 (4.5)	1 (11.1)	0 (0.0)	1 (3.6)	3 (3.4)	0.236
Family asthma history	4 (18.2)	3 (33.3)	13 (43.3)	5 (17.9)	25 (28.1)	0.107
Physical findings						
Body temperature °C, median (range)	38.5 (35.9–40.4)	38.6 (37.2–38.8)	38.6 (36.5–40.3)	38.6 (36.2–40.2)	38.6 (35.9–40.4)	0.729
SpO_2¶ -%, median (tange)	96.5 (87–98)	91.0 (86–97)	90.0 (82–97)	93.0 (74–98)	92.0 (74–98)	<0.001
Co-infection‖ - No. (%)	6 (27.3)	7 (77.8)	14 (46.7)	13 (46.4)	40 (44.9)	0.081
Laboratory findings – median (range)						
WBC ($10^3/\mu L$)	6730 (3260–13980)	15810 (6100–13450)	8000 (2790–16280)	6820 (900–15580)	7740 (900–16280)	0.056
Hemoglobin (g/dL)	13.3 (10.2–16.8)	13.2 (12.0–17.5)	13.4 (4.9–14.9)	13.4 (10.7–15.6)	13.4 (4.9–17.5)	0.911
Platelet ($10^3/\mu L$)	20.3 (8–39)	26.6 (17–44)	23.8 (14–193)	23.2 (12–135)	22.9 (8–193)	0.103
LDH (U/L)	240.5 (168–407)	287.0 (239–397)	270.5 (218–418)	264.5 (183–438)	265.0 (168–438)	0.057
ALP (U/L)	513.5 (7–1173)	748 (240–1091)	620 (449–1008)	603 (123–756)	614.0 (7–1173)	0.224
AST (U/L)	28.0 (16–79)	31.0 (25–50)	29.0 (19–45)	27.0 (21–100)	29.0 (16–100)	0.235
ALT (U/L)	15.0 (8–33)	18.0 (14–33)	13.5 (10–34)	14.5 (8–70)	15.0 (8–70)	0.016
Creatinine (mg/dL)	0.44 (0.22–1.01)	0.3 (0.21–1.03)	0.35 (0.18–0.91)	0.41 (0.26–2.69)	0.40 (0.18–2.69)	0.087
Sodium (mEq/L)	135.0 (129–141)	136 (133–138)	135 (130–141)	135.5 (126–140)	135.0 (126–141)	0.364
Potassium (mEq/L)	3.9 (3.4–5.2)	4.1 (3.5–5.0)	4.0 (3.4–4.6)	4.0 83.3–4.4)	4.0 (3.3–5.2)	0.698
CRP (mg/dL)	0.91 (0–11)	0.83 (0.19–2.06)	1.91 (0.05–9.23)	1.0 (0.07–10.41)	1.17 0.0–11.04)	0.271
Total serum IgE (U/mL)	101.0 (21–6691)	74.0 (3–382)	473.5 (1–9179)	283.0 (25–3440)	243.0 (1–9179)	0.164

*Wheezing was defined as a continuous high pitched sound emitting from the chest during expiration on auscultation.
†Pneumonia was diagnosed on the basis of infiltrative shadows on chest radiograph.
‡Asthma includes active asthma and inactive asthma.
§Other comorbidities include smoking , alcoholism, diabetis meritis, chronic heart diseases , obesity.
¶SpO_2: oxygen saturation measured by pulse oximetry in room air.
‖Pathogenic bacteria co-infection was detected by throat swabs and/or sputum.
Definition of abbreviations: WBC, white blood cell count; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine aminotransferase; CRP, C-reactive protein; IgE, Immunoglobulin E.
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presenting with wheezing, revealed that early systemic corticosteroid treatment did not result in negative clinical outcomes if patients were treated with antiviral agents during the early stage of illness.

Although asthma is not the only illness that causes wheezing, asthma is a risk comorbidity for influenza A(H1N1)pdm09 [8]. In the present study, wheezing was observed in 43.8% of all subjects, including in subjects who presented with pneumonia (Table 1). Systemic corticosteroid treatment is recommended in the asthma guidelines for treating acute exacerbation of asthma which requires hospitalization [9,10,11], but its use remains uncertain for asthma-exacerbated patients with pneumonia due to influenza A(H1N1)pdm09 [1,2,3].

The healthcare seeking behavior for people in Japan is customarily early especially for acute diseases including pandemic influenza and a median days to the initiation of treatment with antiviral agents from the symptom onset was 1.9 days (range, 1–7) in the study subjects (Table 2). The previous study in Mexico reported that the earlier administration of antiviral agent reduced severity of pneumonia, occurrence of pneumonia, and the duration of hospitalization [15]. In the present study, the study subjects were not admitted in the ICU, did not require mechanical ventilation support, and the median of duration of hospitalization was 7 days (range, 2–14) (Table 1). These results indicated that the study subjects, who were mostly young and were initiated the

Table 2. Treatment and clinical time course of study subjects.

	Upper respiratory tract infection	Wheezing* illness	Pneumonia[†¶] with wheezing	Pneumonia without wheezing	Total	P value
Number of subjects (%)	22 (24.7)	9 (10.1)	30 (33.7)	28 (31.5)	89 (100.0)	0.007
Treatments						
Time to initiation of antiviral agents from symptom onset - median days (range)	1.8 (1–3)	1.7 (1–3)	2.4 (1–5)	1.6 (1–7)	1.9 (1–7)	0.054
Antiviral agents						0.006
Oseltamivir	12 (54.5)	7 (77.8)	22 (73.3)	12 (42.9)	53 (59.6)	
Zanamivir	9 (40.9)	2 (22.2)	7 (23.3)	13 (46.4)	31 (34.8)	
Both oseltamivir and zanamivir[‡]	1 (4.5)	0 (0.0)	1 (3.3)	3 (10.7)	5 (5.6)	
Systemic corticosteroid treatment[§]	4 (18.2)	7 (77.8)	28 (93.3)	18 (64.3)	57 (64.0)	<0.001
Time to initiation of systemic corticosteroids from symptom onset - median days (range)	2.0 (2–2)	2.0 (1–5)	2.4 (1–6)	1.8 (1–5)	2.1 (1–6)	0.134
Duration of systemic corticosteroid treatment-median days (range)	5.0 (4–6)	3.3 (2–6)	5.8 (3–9)	4.4 (2–8)	5.2 (2–9)	<0.001
Anti-asthma agents other than corticosteroid[¶]	6 (27.3)	9 (100.0)	30 (100.0)	21 (75.0)	66 (74.2)	<0.001
Oxygen supply[‖]	7 (31.8)	5 (55.6)	19 (63.3)	19 (67.9)	50 (56.2)	0.002
Antibiotics**	8 (36.4)	8 (88.9)	28 (93.3)	19 (67.9)	63 (70.8)	<0.001
Clinical time course						
Time to fever alleviation* - hours, median (range)	35.4(11–120)	44.0 (14–116)	32.0 (12–150)	37.3 (9–168)	35.0 (9–168)	0.967
Length of Hospitalization, days, median (range)	4.9 (2–9)	6.8 (3–10)	8.4 (6–14)	7.6 (3–14)	7.5 (2–14)	<0.001

*Wheezing was defined as a continuous high pitched sound emitting from the chest during expiration on auscultation.
†Pneumonia was diagnosed on the basis of infiltrative shadows on chest radiograph.
‡Antiviral medication was switched oseltamivir to zanamivire and vice versa.
§The dose of corticosteroid was equivalent to methylprednisolone 1.0–1.5 mg/body weight (kg)/time, 2–4 times/day, in subjects under 15 years of age, and 40–80 mg/time, 2–4 times/day in those over 15 years of age.
¶At least one medication of shortacting β2-agonist, longacting β2-agonist, inhaled isoproterenol, inhaled disodium cromoglycate, aminophylline, and leukotriene receptor antagonists.
‖Oxygen was administered using a nasal cannula or face mask.
**Antibiotics.
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treatment with antiviral agents earlier, did not progress to be critical.

Most subjects presented with respiratory disorders, including upper respiratory tract infection, wheezing illness, and pneumonia with or without wheezing. Wheezing is one of the manifestations of asthma and a previous report indicated that wheezing is associated with influenza mortality [16]. In the present study, total 43.8% of subjects presented wheezing and 33.7% presented both pneumonia and wheezing. Also, asthma history was more frequent among subjects with wheezing illness (55.6%) or pneumonia with wheezing (43.3%) than among the other subjects in upper respiratory infection (13.6%) and pneumonia without wheezing (17.9%) (Table 1). The results indicated that the occurrence of exacerbation of asthma might have been increased by influenza A(H1N1)pdm09 in this study population; however, exacerbation of asthma did not became critical. Systemic corticosteroid was mainly used for patients with wheezing either with pneumonia or without pneumonia. The presentation of wheezing can lead to a diagnosis of asthma if the patients have a history of asthma. Also, wheezing could also indicate a first episode of asthma attack or bronchiolitis, which are difficult to distinguish on the basis of wheezing alone. If a patient has asthma acute exacerbation or a first episode of asthma attack, not using systemic corticosteroids can increase disease severity and mortality [9,10,11]. Therefore, systemic corticosteroid treatment should be a consideration for clinical management of patients with wheezing despite the presence of viral pneumonia and/or bronchiolitis. Also, anti-asthmatic agents other than systemic corticosteroids were administered to all subjects with wheezing (Table 2). Treatments with anti-asthmatic agents together with corticosteroids need to be included as well as antibiotic agents in case of bacterial co-infection.

Respiratory condition, as reflected by SpO_2, was more severe in subjects of the steroid group than in the non-steroid group (Table 3). Also, oxygen was more supplied to the steroid group. Those results described that respiratory condition was more severe in the steroid group; however, systemic corticosteroid treatment has no influence to hours to fever alleviation after the initiation of treatment with antiviral agents and the duration of hospitalization (Table 3). In terms of assessment of clinical time course, the Kaplan-Meier curves for hours to fever alleviation from the initiation of antiviral agents and hospitalization days were not significantly different between the steroid and the non-steroid groups. (Figure 2). Systemic corticosteroids were administered for the most of subjects with wheezing (Table 2). These results suggests that systemic corticosteroid treatment for viral pneumonia with wheezing may not have negative effects to clinical time course.

Multiple logistic regression analysis among subjects with respiratory disorders evaluated that wheezing, pneumonia, and SpO_2 were independent factors associated with using systemic corticosteroid treatment (Table 4). The results indicated that these were factors that could motivate physicians to start systemic

Table 3. Clinical presentation of subjects with pneumonia according to systemic corticosteroid treatment.

	Steroid group*	No-steroid group*	Total	P value
Number of subjects No. (%)	46 (100)	12 (100)	58 (100)	
Symptoms and signs on admission				
Wheezing† -No. (%)	27 (58.7)	1 (8.3)	28 (48.3)	0.002
Co-infection‡-No. (%)	24 (52.2)	3 (25.0)	27 (46.6)	0.093
Body temperature -°C, median (range)	38.6 (36.5–40.3)	38.2 (36.2–40.2)	38.6 (36.2–40.3)	0.261
Laboratory findings on admission, median (range)				
SpO_2§ (%)	90.0 (74–97)	95.6 (91–98)	91.0 (74–98)	<0.001
WBC ($10^3/\mu L$)	8200 (2790–16280)	6385.0 (900–13280)	7715.0 (900–16280)	0.024
LDH (U/L)	270 (201–418)	255.5 (183–438)	267.5 (183–438)	0.687
CRP (mg/dL)	1.16 (0.05–9.23)	2.69 (0.07–10.41)	1.22 (0.05–10.41)	0.154
Sodium (mEq/L)	135.1 (130–141)	134.8 (126–139)	135 (126–141)	0.734
Potassium (mEq/L)	3.96 (3.3–4.6)	3.39 (3.3–4.5)	3.95 (3.3–4.6)	0.438
Treatment -No. (%)				
Days to administration of antiviral agents¶	2.0 (1–5)	1.8 (1–7)	2.0 (1–7)	0.589
Anti-asthma treatments‖	45 (97.8)	6 (50.0)	51 (87.9)	<0.001
Antibiotic agents	41 (89.1)	6 (50.0)	47 (81.0)	0.006
Oxygen supply**	45 (97.8)	1 (8.3)	46 (79.3)	<0.001
Clinical outcomes, median (range)				
Hours to alleviation of fever after admission††	36.0 (9–150)	35.5 (9–168)	35.5 (9–168)	0.611
Hospitalization days	8.2 (5–14)	7.7(3–14)	8.1 (3–14)	0.607

N = 58.
*No-steroid and steroid group denote group of subjects who were not treated and treated with systematic corticosteroids.
†Wheezing was defined as a continuous high pitched sound emitting from the chest during expiration on auscultation.
‡Pathogenic bacteria co-infection was detected by throat swabs and/or sputum.
§SpO_2: oxygen saturation measured by pulse oximetry in room air.
¶The number of days from symptom onset to the initiation of administration of antiviral agent either oseltamivir or zanamivir.
‖At least one medication of short-acting β2-agonist, long-acting β2-agonist, inhaled isoproterenol, inhaled disodium cromoglycate, aminophylline, and leukotriene receptor antagonists.
**Oxygen was administered using a nasal cannula or face mask.
††The time (hours) to alleviation of fever to less than 37°C after the administration of antiviral agents.
Definition of abbreviation: WBC, white blood cell count; LDH, lactate dehydrogenase; CRP, C-reactive protein.
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corticosteroid treatment at the study site. It also indicated that wheezing was not the only factor for using systemic corticosteroid treatment but also pneumonia and low level of respiratory condition which were reflected by SpO_2. In the present study, systemic corticosteroid treatment did not produce negative outcomes, even in patients with pneumonia and might be in patients with bronchiolitis. The results showed that the systemic corticosteroid treatment in the early stage of illness together with antiviral agents might work to reduce the time of critical conditions and to prevent disease progression to severe pneumonia among patients who were administered antiviral agents during the early stage of illness when their pneumonia were not so severe (Table 2).

Although secondary bacterial infection was reported as a negative outcome of systemic corticosteroid treatment in the severe ill patients with influenza H1N1pdm09 [2], in the present study, no significant effects of systemic corticosteroid treatment against bacterial co-infection were observed. It might be resulted from the antibiotics treatment from the hospital admission (Table 2, 3) and can be explained by the short duration of hospitalization of study subjects. (Table 2, 3).

Limitations of the present retrospective study are that the influenza HN1 2009 virus was confirmed in the limited number of subjects by RT-PCR and patients strongly considered to have 2009 influenza A/H1N1 virus infection were included. During the study period, influenza A(H1N1)pdm09 virus was the dominant influenza virus in Japan according to the Infectious Agent Surveillance Report in Japan [17]. Subjects who were identified as having influenza A virus infection were strongly considered to have influenza A(H1N1)pdm09 virus infection, so physicians diagnosed those patients as having influenza A(H1N1)pdm09 infection. Also, most of the study subjects were pediatric patients and the age distribution of the study subjects was representative of that for influenza A(H1N1)pdm09 in Japan [17,18]. The number of subjects in divided four groups according to the respiratory conditions were not equal as well as the small number of subjects without steroids treatment due to the retrospective study in a single hospital. Therefore, the further prospective study in patients with a variety of ages with large population is needed.

In conclusions, systemic corticosteroid treatment together with early administration of antiviral agents did not result in negative clinical outcomes in patients with influenza viral pneumonia with wheezing and without wheezing in the present study. The findings suggest that influenza pneumonia patients with wheezing and potentially without wheezing could be treated by systemic corticosteroids and early administration of antiviral agents if the severity of disease is before critical condition.

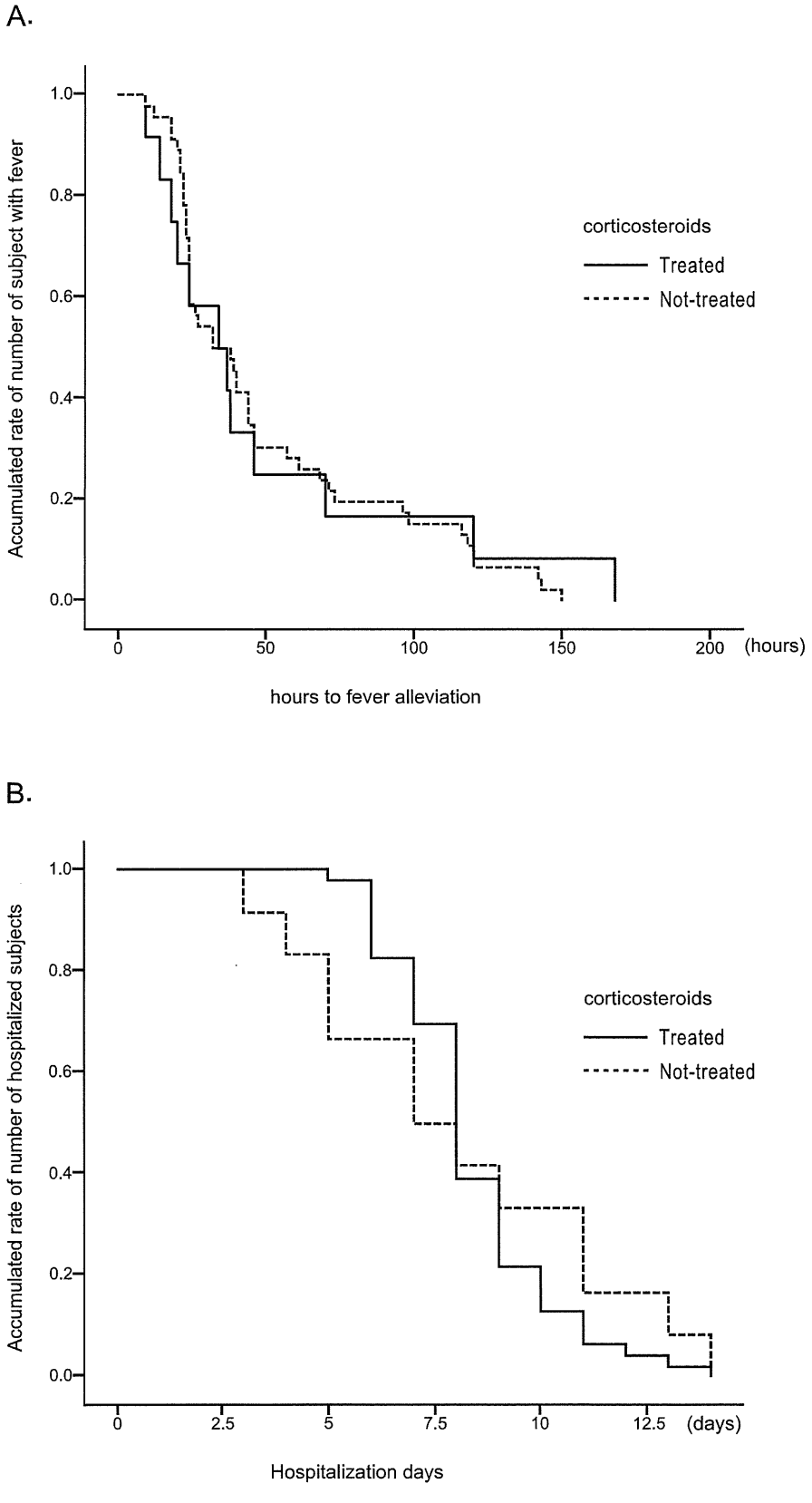

Figure 2. Systemic corticosteroids treatment in the relation0 to clinical time course assessed by Kaplan-Meier methods. Kaplan-Meier curves of the number of hours to fever alleviation (A) and hospitalization days (B) according to systemic corticosteroid treatment among subjects with viral pneumonia in steroid (n = 46) and non-steroid (n = 12) groups There were no significant differences between the groups in terms of either hours to fever alleviation (log rank test, p = 0.835) or hospitalization days (log rank test, p = 0.626).
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Table 4. Clinical factors for using systemic corticosteroids treatment among the study subjects by multiple logistic regression analysis.

Parameter	Regression coefficient	Standard error	P value	Odds ratio	95% confidence interval
Intercept	20.444	8.927			
Wheezing*	2.401	0.841	0.004	11.03	2.12–57.33
Pneumonia†	1.298	0.618	0.036	3.66	1.09–12.30
SpO2‡	−0.229	0.094	0.015	0.80	0.66–0.96

n = 89.
*Wheezing was defined as a continuous high pitched sound emitting from the chest during expiration on auscultation.
†Pneumonia was diagnosed on the basis of infiltrative shadows on chest radiograph.
‡SpO_2: oxygen saturation measured by pulse oximetry in room air on admission.
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Author Contributions

Conceived and designed the experiments: KK. Performed the experiments: KK JT HU RY TM EK NK TJM. Analyzed the data: TM KK. Wrote the paper: KK TM.

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ORIGINAL ARTICLE

A national survey on myocarditis associated with influenza H1N1pdm2009 in the pandemic and postpandemic season in Japan

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Abstract An influenza pandemic occurred in 2009. We performed a retrospective national questionnaire survey about H1N1pdm2009 myocarditis to compare influenza A H1N1pdm2009 myocarditis in the pandemic (2009/2010) and postpandemic seasons (2010/2011) by collecting data from 360 hospitals. The diagnosis of myocarditis was performed using the guidelines for Diagnosis and Treatment of Myocarditis published by the Japanese Circulation Society (JCS 2009). Twenty-nine patients with influenza A H1N1pdm2009 myocarditis were reported, with 25 from the 2009/2010 season and only 4 patients from the 2010/2011 season. Morbidity and mortality was 28 % (8/29) among all the myocarditis patients. Six patients with myocarditis were complicated by pneumonia. Myocarditis was proved by endomyocardial biopsy or autopsy in 9 patients, although histological findings showed mild myocarditis even in clinically defined fulminant myocarditis cases. Seventeen patients were diagnosed with fulminant H1N1pdm2009 myocarditis with fatal arrhythmias or varying degrees of cardiogenic shock. Fifteen fulminant myocarditis patients were seen in the 2009/2010 season and only 2 in the 2010/2011 season. Ventilators were used in 16 patients. Mechanical circulatory support with intraaortic balloon pumping or percutaneous cardiopulmonary support (IABP/PCPS) was emergently inserted in 13 patients. Of these, 9 patients were rescued with mechanical circulatory support, and 4 patients died. Four fulminant myocarditis patients treated without IABP/PCPS died. We described the clinical features of patients with myocarditis associated with influenza H1N1pdm2009 in the pandemic and postpandemic seasons and demonstrated the high prevalence of fulminant myocarditis (17/29, 59 %). The number of patients with myocarditis associated with influenza A virus seemed to increase in the pandemic season.

Keywords Myocarditis · Influenza A · Pandemic

Introduction

Acute myocarditis is a potentially lethal disease: the etiological agents of viral myocarditis include enteroviruses, adenoviruses, parvoviruses, cytomegalovirus, and influenza viruses [1–7]. Fulminant myocarditis causes severe hemodynamic dysfunction that requires high-dose catecholamine and mechanical circulatory support [1, 7]. Although the frequency of myocardial involvement in influenza infection is variable, that of fulminant myocarditis associated with influenza infection is rare, as shown in previous papers [1–4]. An influenza pandemic occurred in 2009 [8–12]. The Ministry of Health, Labor and Welfare of Japan (MHLW) confirmed only 198 deaths among about 20.61 million patients infected with influenza A H1N1pdm2009 in the 2009/2010 season and 150 deaths among about 10.3 million patients in the 2010/2011 season in Japan [10, 11]. Although usually

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both the diagnosis and treatment of the pathogen involved in myocarditis are difficult, in the 2009/2010 pandemic, adequate diagnostic methods, such as the rapid influenza tests and reverse transcription-polymerase chain reaction (RT-PCR) for influenza H1N1pdm2009, and treatment with neuraminidase inhibitors were already available [10–13]. By conducting a cross-sectional national survey with assistance from all members of the Japanese Circulation Society (JCS) in the 2009/2010 influenza season, we previously reported 15 H1N1pdm2009 myocarditis patients and demonstrated their clinical features [13]. The Japanese Circulation Society performed a prospective study of patients with myocarditis associated with H1N1pdm2009 in the 2010/2011 season using their website, although no case was reported. Therefore, to compare myocarditis associated with influenza H1N1pdm2009 in the pandemic (2009/2010) and post-pandemic (2010/2011) seasons, we performed a national survey with a fill-in-the-blanks and multiple-choice questionnaire mailed to hospitals in Japan that have cardiology or pediatric departments or both.

Patients and methods

We mailed questionnaires to 978 hospitals in Japan that have cardiology and pediatric departments to compare myocarditis associated with influenza H1N1pdm2009 in the pandemic (2009/2010) and postpandemic (2010/2011) seasons. A fill-in-the-blanks and multiple-choice questionnaire was designed to obtain information on patient profiles (sex, age, and baseline disease), symptoms of influenza, symptoms of myocarditis, laboratory findings (e.g., cardiac enzymes, ECG, echocardiogram), treatment (e.g., neuraminidase inhibitors, steroid, mechanical circulatory support, ventilator), outcomes, and other. The questionnaire also included information about the number of hospitalizations associated with H1N1pdm2009 influenza during the two seasons. Myocarditis was diagnosed using the Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009) [1]. Compatible clinical symptoms, echocardiographic abnormalities in the absence of cardiac ischemia, and leakage of cardiac enzymes or other evidence of myocardial damage aided the diagnosis of myocarditis. Laboratory diagnosis of influenza A H1N1pdm2009 was made by quick influenza diagnostic testing or probe-based RT-PCR using a nasopharyngeal swab or sputum. The study protocol was approved by the Institutional Review Board of Osaka Medical College.

Results

We received completed questionnaires from 360 hospitals. Although 25 patients with myocarditis associated with influenza H1N1pdm2009 (17 men and 8 women; mean age, 39 ± 21 years) were reported to the task force of the Clinical Research for Myocarditis in the pandemic season (2009/2010), only 4 patients (3 men and 1 woman; mean age, 45 ± 15 years) were reported in the postpandemic season (2010/2011). Total mortality rate among all the myocarditis patients in both seasons was 28 % (8/29). Patient profiles, laboratory findings, treatments, and outcomes of patients with myocarditis associated with H1N1pdm2009 are shown in Table 1.

Myocarditis was proved by endomyocardial biopsy or autopsy in 9 patients (31 %); it was clinically diagnosed based on clinical features, leakage of cardiac constitutional proteins, such as troponin T/I, abnormalities on echocardiography, and other findings in the other 20 patients. Cardiac symptoms such as dyspnea, chest discomfort, hypotension, and syncope developed within 3 days of sickness in 16 patients (64 %). The most frequent baseline disease was a respiratory disorder in 7 (24 %) patients, including bronchial asthma in 5 patients (17 %) and emphysema in 2 patients (8 %). Six patients (21 %) with myocarditis were complicated by pneumonia. RT-PCR or quick diagnostic testing yielded positive results in all patients (100 %). Most patients exhibited ECG abnormalities, such as ST-T abnormalities (64 %). Echocardiography revealed abnormalities of left ventricular wall motion in 24 patients (83 %). Seven of the 9 patients of histologically proven myocarditis were fulminant myocarditis patients; 2 had acute myocarditis. Histological findings of these 9 patients showed myocarditis with lymphocyte infiltration. Quantitative assessment of troponin T/I was performed in 5 patients, in all of whom (100 %) it was elevated. On the other hand, qualitative quick troponin testing, which was conducted in 6 patients, was positive in only 3 patients (50 %). Cardiovascular magnetic resonance imaging (MRI) was performed in 2 patients. T_2-weighted cardiovascular MRI showed high-density signals in the region of the left ventricle in a 28-year-old man with fulminant myocarditis; his serial biopsies showed mild inflammation and degeneration of myocytes. RT-PCR testing for H1N1pdm2009 from heart specimens was performed in 2 cases (8 %), in both of whom it was negative. Cardiac dysfunction almost completely resolved in 19 patients (66 %) but remained partly unresolved in 2 patients (8 %). Coronary studies, which were performed in 20 patients (69 %), yielded normal results in all. Twenty-eight patients (96 %) were treated with neuraminidase inhibitors.

Seventeen of the 29 patients (59 %) were diagnosed with fulminant myocarditis with fatal arrhythmias and/or varying degrees of cardiogenic shock. Fifteen fulminant myocarditis patients (15/25, 60 %) were seen in the 2009/2010 season and only 2 (2/4, 50 %) in the 2010/2011 season. The clinical data of these 17 fulminant myocarditis patients are shown in Table 2. Nine (53 %) of the 17 fulminant myocarditis

Table 1 Patient profiles, laboratory findings, results of endomyocardial biopsies and/or autopsies, treatments, and outcomes of patients with myocarditis associated with H1N1pdm2009 in the 2009/2010 and 2010/2011 influenza seasons in Japan

	2009/2010 season	2010/2011 season
Number of H1N1pdm myocarditis cases	25	4
Sex (male/female)	17 (68 %)/8 (32 %)	1 (25 %)/3 (75 %)
Age (mean ± SD)	39 ± 21	45 ± 15
Survival	19 (76 %)	2 (50 %)
Adult/children	20 (80 %)/5 (20 %)	4 (100 %)/0 (0 %)
Fulminant myocarditis (adult/child)	15 (60 %) (11/4)	2 (50 %) (2/0)
Biopsy/autopsy	10 (40 %)/3 (12 %)	0/1 (25 %)
Baseline disease	Asthma, emphysema 6 (24 %)	Asthma 1 (25 %)
	DM 2 (8 %)	Hypertension 1 (25 %)
	None 14 (56 %)	None 1 (25 %)
Pneumonia	Viral 2 (8 %)/bacterial 2 (8 %)	Viral 1 (25 %)/bacterial 1 (25 %)
Cardiac symptoms	Dyspnea 13 (52 %)	Dyspnea 3 (75 %)
	Chest pain 4 (16 %)	Shock 1 (25 %)
	Syncope 3 (12 %)	Cyanosis 1 (25 %)
Onset of cardiac symptoms	1st–3rd day of sickness 16 (64 %)	1st–3rd day of sickness 0 (0 %)
	4th–10th day of sickness 6 (24 %)	4th–10th day of sickness 4 (100 %)
	Over 11th day of sickness 3 (12 %)	Over 11th day of sickness 0 (0 %)
ECG abnormalities	ST-T abnormalities 16 (64 %)	PSVT 2 (50 %)
	VT, VF 5 (20 %)	WNL 1 (25 %)
	Complete AV block 3 (12 %)	
	No information 2 (8 %)	No information 1 (25 %)
Echocardiogram	Wall motion abnormalities 21 (84 %)	Wall motion abnormalities 3 (75 %)
	Pericardial effusion 3 (12 %)	Pericardial effusion 1 (25 %)
	No information 2 (8 %)	No information 1 (25 %)
Peak CPK values	13,639 ± 42,495 IU/l	14,604 ± 18,770 IU/l
Coronary artery (CAG/CT)	No stenosis 15 (60 %)	No stenosis 3 (75 %)
	Not examined 10 (40 %)	Not examined 1 (25 %)
Other diagnostic tool (positive/examined)	Qualitative troponin 3/6 (50 %)	Qualitative troponin 0/0
	Quantitative troponin T/I 5/5 (100 %)	Quantitative troponin T/I 0/0
	MRI 1/2 (50 %)	MRI 0/0
Antiviral drug	24 (96 %)	4 (100 %)
Other treatment	Steroid 5 (20 %)	Steroid 0 (0 %)
	γ-Globulin 6 (24 %)	γ-Globulin 0 (0 %)

patients had no baseline disease. Three fulminant myocarditis patients (17 %) were complicated by pneumonia. Myocarditis was proved by endomyocardial biopsy or autopsy in 7 (41 %) of the 17 fulminant myocarditis patients. Histological findings were classified by the Dallas Criteria [14]. The first biopsy, obtained from a 44-year-old woman on day 1 showed myocarditis with lymphocytic infiltration, degeneration of myocytes, and interstitial edema; the second biopsy on day 23 showed resolving myocarditis. Histological findings in the other 8 patients showed myocarditis with infiltration of lymphocytes (ranging from mild to moderate, but not severe). Autopsy of the patient with fulminant myocarditis (on day 9) showed only interstitial fibrosis without lymphocytic infiltration. Ventilators were used in 16 patients (94 %). Mechanical circulatory support with intraaortic balloon pumping (IABP) and/or percutaneous cardiopulmonary support (PCPS) was emergently inserted in 13 patients. Nine of

Table 2 Patient profiles, laboratory findings, reports of endomyocardial biopsies and/or autopsies, treatments, and outcomes of patients with fulminant myocarditis associated with influenza A H1N1pdm2009 in Japan

	Fulminant myocarditis
Number of cases (adult/children)	17 (13/4)
Sex (male/female)	10 (58 %)/7(42 %)
Age (mean ± SD)	32 ± 19
Survival	9/17 (53 %)
Baseline disease	Asthma, emphysema 4 (24 %)
	DM 2 (12 %)
	None 9 (53 %)
Complicated pneumonia	3 (18 %)
Histological findings of heart tissue by Dallas criteria (1987) [14]	Resolving myocarditis (1st biopsy on day 1: myocarditis, LI, IE, MD; 2nd biopsy on day 23: LI)
	Myocarditis on day 1 (moderate LI, IE, MD)
	Myocarditis on day 1 (moderate LI, IE, MD)
	Myocarditis on day 4 (mild LI, IE, MD)
	Myocarditis on day 32 (mild LI, IE, MD)
	Borderline myocarditis (LI)
	Borderline myocarditis on day 7 (LI)
	No myocarditis on day 9 (IF)
	No myocarditis on day 16 (IF)
RT-PCR from heart tissue	0/2 (0 %) (on days 8 and 9)
Peak CPK values	23,640 ± 52,471 IU/l
Other diagnostic tool (positive/examined)	Qualitative troponin 2/3 (67 %)
	Quantitative troponin T/I 5/5 (100 %)
	MRI 1/2 (50 %)
Ventilator	15 (88 %)
IABP/PCPS	13 (76 %)
Survival with IABP/PCPS	9/13 (69 %)
Antiviral drug	16 (96 %)

Histological findings were classified by the Dallas Criteria [14]. First biopsy: myocarditis, borderline myocarditis, no myocarditis. Subsequent biopsies: ongoing myocarditis, resolving myocarditis, resolved myocarditis

LI lymph node infiltration, *IE* interstitial edema, *DM* diabetes mellitus, *MD* degeneration of myocyte, *IF* interstitial fibrosis

these 13 patients (69 %) were successfully rescued with mechanical circulatory support; the remaining 4 patients died (31 %). Four fulminant myocarditis patients treated without IABP/PCPS also died (100 %).

Discussion

The MHLW of Japan confirmed only 198 deaths (9.6×10^{-4} %) among about 20.61 million patients infected with influenza A H1N1pdm2009 in the 2009/2010 season, and 150 deaths (15×10^{-4} %) among about 10.3 million patients in the 2010/2011 season in Japan [10, 11]. The low case-fatality rate in Japan may be a result of early diagnosis and aggressive early intervention with antiviral drugs [9–11]. Twenty-five influenza H1N1pdm2009 myocarditis patients ($\geq 0.20 \times 10^{-4}$ %) were reported in the 2009/2010 season, although only 4 patients ($\geq 0.031 \times 10^{-4}$ %) were documented in the 2010/2011 season in the present study. The number of patients with clinically defined myocarditis associated with the influenza A virus seemed to increase in the pandemic season and obviously decrease in the postpandemic season compared to the pandemic season [2–4, 12, 13, 15–17]. The mean age (39 years) of myocarditis patients associated with H1N1pdm2009 influenza seemed to be lower than the age of patients with serious illness associated with seasonal influenza in the present study, probably indicating an age shift to a younger population in myocarditis patients with high fatality.

The frequency of myocardial involvement in influenza infection is variable, with fulminant myocarditis associated with seasonal influenza infection being rare, as shown in previous papers, probably because of the low affinity of the influenza virus for the myocardium [1–6]. Small autopsy-based studies demonstrated the complication rate of focal to diffuse myocarditis in fatal cases as 39 % with the 1957 Asian influenza pandemic and 48 % with the Spanish influenza pandemic [2]. Myocarditis caused by influenza is likely to be a terminal event in patients during influenza pandemics. In our survey, a total of 17 fulminant myocarditis patients were reported, 8 of whom died (47 %), although fulminant myocarditis caused by influenza infection is an uncommon type of myocarditis. We demonstrated a high prevalence of fulminant myocarditis

among all the myocarditis patients (17/29, 59 %). We found that, along with pneumonia and encephalopathy, myocarditis was an important cause of clinical deterioration in patients infected with H1N1pdm2009 in Japan [9, 10, 13, 15]. The influenza A virus might be more commonly associated with severe forms of myocarditis in the pandemic season than other seasons [2–4, 13, 15–17]. Because there was no significant difference in the H1N1pdm2009 virus in the 2009/2010 and 2010/2011 seasons [10, 12], we speculate that the pathological mechanism of influenza myocarditis differs depending on the pathogen, and may depend on host immunity, as indicated by anti-H1N1pdm2009 titers.

In our study, quantitative values of troponin I/T were elevated in all five patients in whom it was measured (100 %). Conversely, the qualitative quick troponin test was positive in only three of the six patients (50 %) in whom it was measured. Hence, we recommend that quantitative troponin I/T assays may be useful for the diagnosis and management of myocarditis.

Many kinds of viruses have been implicated as causes of myocarditis, with different viruses having different potentials to cause myocarditis [2–7, 12, 13, 15–17]. In their study, Bowles et al. reported that endomyocardial biopsy samples from 624 patients with clinically defined myocarditis were analyzed by PCR to detect various viral genes, of which 239 samples were positive [4]. Adenovirus was detected from 142 samples, enteroviruses from 85 samples, cytomegalovirus from 18 samples, and influenza A from 5 samples (0.8 %) [4]. In the present study, RT-PCR testing for H1N1pdm2009 from heart specimens were negative in both patients in which it was performed. Although it is well known that coxsackie viruses present a high affinity for cardiac myocytes, the pathological effects of influenza virus myocarditis in humans and mice are reportedly milder than coxsackie virus myocarditis and are more localized [4–6, 18]. The affinity of the influenza virus for cardiac myocytes is also reportedly low [3, 4, 6, 18]. Pan et al. reported the molecular mechanism of myocarditis associated with the influenza virus and revealed the importance of trypsin induction and increased production of pro-inflammatory cytokines in the pathogenesis of acute myocarditis [17–20]. Besides the direct effect of influenza virus infection, pro-inflammatory cytokines are thought to contribute to the pathogenesis of severe clinical features, including severe cardiac dysfunction, in influenza patients [13, 15, 18–21].

Myocarditis was proved by endomyocardial biopsy or autopsy in nine patients in this study, although the pathological findings were mild even in clinically defined fulminant myocarditis patients. A new approach to diagnosing myocarditis is cardiovascular magnetic resonance imaging (MRI) [1, 15]. MRI was indicative of myocarditis in one of two (50 %) patients in this study in whom it was performed. Hence, MRI might be more useful than invasive cardiac biopsy for diagnosing H1N1pdm2009 myocarditis and for estimating the activity and severity of inflammation, although further evaluation of its diagnostic efficacy is recommended.

There are some limitations to this study. We planned a statistical analysis between the number of myocarditis patients and the number of hospitalizations associated with H1N1pdm2009 influenza. However, this was not possible because of the low response rate to the question about the number of hospitalizations (responses were obtained from only 40 hospitals); further, many hospitalizations in the 2009/2010 season were for social reasons rather than serious illness.

Our study suggests that because cardiac symptoms developed within 3 days of sickness in 17 patients and cardiac dysfunction rapidly progressed in H1N1pdm2009 myocarditis, early diagnosis and prompt treatment of acute myocarditis with heart failure is required in patients with influenza infection during the pandemic season. Appropriate intervention in patients with fulminant influenza myocarditis consists of treatment with neuraminidase inhibitors to eliminate the causative virus, and mechanical circulatory support [intraaortic balloon pumping (IABP)/ percutaneous cardiopulmonary support (PCPS)] to treat the depressed myocardial function [1, 7, 12, 13, 15].

In conclusion, we confirmed the clinical features of patients with clinically defined myocarditis associated with influenza H1N1pdm2009 and demonstrated the high prevalence of fulminant disease (17/29, 59 %) in patients with influenza myocarditis. The number of patients with myocarditis associated with influenza A virus seemed to increase in the pandemic season but not in the nonpandemic season.

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Conflict of interest None declared.

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