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Original Article

Clinical Manifestations of Patients with Influenza Differ by Age: A Prospective, Multi-centered Study in the Setouchi Marine Area

Ryosuke Takase, Hideharu Hagiya*, Hiroyuki Honda, Yasuhiro Nakano, Hiroko Ogawa, Mikako Obika, Keigo Ueda, Hitomi Kataoka, Yoshihisa Hanayama, and Fumio Otsuka

Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

Influenza potentially has a high mortality rate when it affects the elderly. We aimed to examine the differences in clinical manifestations in patients with influenza according to their age. This multicenter prospective study was performed in six medical institutions in Okayama and Kagawa prefectures (Japan). Between December 1, 2019 and March 31, 2020, we collected data on adult patients diagnosed with influenza type A, who were stratified into younger (20-49 years), middle-aged (50-64 years), and older groups (≥65 years). We compared the presence or absence of fever, respiratory symptoms, and extrapulmonary symptoms according to age group. In total, 203 patients (113, younger; 51, middle-aged; and 39, older) were eligible for the analysis. The maximum body temperature and temperature at first physician visit in the older group were significantly lower than those in the younger group. The incidence of respiratory symptoms was not different among the three groups. Chills, muscle pain, and arthralgia as systemic symptoms were noted significantly more frequently in the younger (80.9%) and middle-aged (75.5%) groups than in the older group (51.3%) ($p = 0.002$). Fever and systemic symptoms were less likely to appear in older patients, possibly resulting in the delaying of hospital visits among older adults.

Key words: influenza, elderly, fever, respiratory symptom

Influenza is a representative viral infection, typically causing an acute-onset high fever accompanied by upper and lower respiratory symptoms such as nasal discharge, sore throat, and cough. According to the statistics from the Ministry of Health, Labour, and Welfare in Japan, >10 million cases of influenza have been reported per year in recent years, while 12 million cases [1] were reported in the 2018–2019 season, with 3,400 deaths [2]. The majority of excess mortality in Japan (the extent to which influenza and pneumonia deaths have increased as a result of the influenza epidemic) [3] was reported in older adults and those who were complicated with cerebrovascular diseases [4]. This finding indicates that influenza will have a great impact on older populations in the hyper-aging society in Japan.

In general, anti-influenza medication is not necessary for young healthy adults infected with influenza because the disease eventually resolves during its course [5]. In contrast, older adults tend to develop more severe disease than younger adults and have a higher incidence of complications such as pneumonia [6]. In fact, 80-90% of influenza deaths occurred in individu-

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*Corresponding author. Phone : +81-86-235-7342; Fax : +81-86-235-7345
E-mail : hagiya@okayama-u.ac.jp (H. Hagiya)

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als aged ≥65 years [7]. However, the clinical symptoms of influenza in the elderly are less apparent or atypical, and early diagnosis is difficult in some cases because the symptoms in the elderly can be vague [8]. From the perspective of preventing the spread of infection, it is also important to establish a diagnosis as early as possible, especially in hospitals and nursing homes in Japan, where the population is aging rapidly.

The differences in influenza symptoms between younger and older populations remain unclear. According to a study on patients with influenza A in nursing homes, upper respiratory symptoms such as sore throat and nasal discharge occurred less frequently in the elderly than in the younger adults, while lower respiratory symptoms such as cough and sputum tended to appear at a higher frequency [9]. However, few studies have investigated the differences in the symptoms of influenza by age. This study aimed to examine and analyze whether the appearance of influenza-related symptoms differs according to age.

Patients and Methods

This was a multicenter prospective study of patients who visited the outpatient clinics in six medical institutions in Okayama and Kagawa prefectures in Japan (Marugame Medical Center, Kasaoka City Hospital, Bizen City National Health Insurance Hospital, Tamano City Hospital, Okayama Kinen Hospital, and Niimi National Health Insurance Yukawa Clinic) between December 1, 2019 and March 31, 2020. Apart from Niimi National Health Insurance Yukawa Clinic, all of these institutions are local general hospitals with inpatient beds. The study protocol was approved by the institutional review board of Okayama University Hospital (Approval No. 1908-017), with prior approval from each institution.

During the influenza pandemic season in Japan, men and women aged 20 years old or older who were suspected of having influenza were included in the study. They were asked to complete a questionnaire-based medical interview sheet to obtain information on the following items: 1) age and gender; 2) vaccination status during the season; 3) axillary body temperature at maximum and at first physician visit; 4) clinical symptoms such as nasal symptoms (nasal discharge, nasal obstruction, and sneezing), pharyngeal symptoms (sore throat, dysphagia, and hoarseness), lower respiratory tract symptoms (cough and sputum), systemic symptoms (chills, muscle pain, and arthralgia), headache, and gastrointestinal symptoms (nausea and diarrhea); and 5) time from disease onset to first physician visit. Written informed consent was obtained from every patient when they answered the self-administered questionnaire.

Patients who were diagnosed with influenza type A using influenza rapid antigen tests were included in the analysis, because influenza type A, not type B, is the major type that causes a pandemic every year in Japan. The eligible patients were divided into three age groups (younger group, 20-49 years; middle-aged group, 50-64 years; and older group, ≥65 years). The primary endpoint was defined as the presence or absence of fever and respiratory symptoms, while the secondary endpoint was the presence of extrapulmonary symptoms (general symptoms, headache, and gastrointestinal symptoms). We also investigated the time from disease onset to first physician visit. These endpoints were compared among the three age groups for analysis.

Statistical analyses were performed using the Kruskal-Wallis test and the Mann-Whitney *U*-test (Bonferroni correction) for continuous variables and Fisher's exact test for categorical variables. Also, to analyze the correlation between age and body temperature, Spearman's rank correlation test was performed. All statistical analyses were performed using EZR software based on R (version 3.5.2). Statistical significance was set at $p < 0.05$.

Results

During the study period, the clinical data of 1,140 patients were collected. Among these patients, 220 were diagnosed with influenza using the rapid influenza antigen test, of whom 207 had influenza type A and 13 had influenza type B. After excluding 4 patients with missing data, 203 were included in the final analysis (Fig. 1).

The background data of patients according to age group are summarized in Table 1. The patients' ages ranged from 20 to 93 years, with a median age of 45.5 years. Overall, 114 men and 89 women were included. The numbers of patients in the younger, middle-aged, and older groups were 113, 51, and 39, respectively. The in-season vaccination rate in the older group was significantly higher (64.7%) than in the younger (29.9%)

and middle-aged (27.9%) groups ($p = 0.001$).

The clinical manifestations of the patients in each age group are also shown in Table 1. The overall mean (± standard deviation) maximum body temperature was 38.4 ± 0.9°C (younger group, 38.5 ± 0.9°C; middle-aged group, 38.3 ± 0.9°C; and older group, 38.2 ± 0.7°C). The overall mean temperature at first physician visit was 37.7 ± 0.9°C (younger group, 37.8 ± 0.9°C; middle-aged group, 37.5 ± 1.1°C; and older group, 37.4 ± 0.9°C). The proportions of patients whose maximum body temperature and temperature at first physician visit were both < 37°C were 3.0%, 9.5%, and 6.1% in the younger, middle-aged, and older groups, respectively. Similarly, the proportions of those whose maximum body temperature and temperature at first physician visit were both < 37.5°C were 13.0%, 19.0%, and 15.2% in the younger, middle-aged, and older groups, respectively. Of 34 elderly patients, the median ages of vaccinated (7 men and 15 women) and unvaccinated (7 men and 5 women) individuals were 74.5 years and 72.8 years, respectively. The maximum body temperatures in the vaccinated (N = 20) and unvaccinated patients (N = 10) were 38.0 ± 0.7°C and 38.4 ± 0.4°C, respectively ($p = 0.07$). Also, the body temperatures at first physician visit in the vaccinated and unvaccinated patients

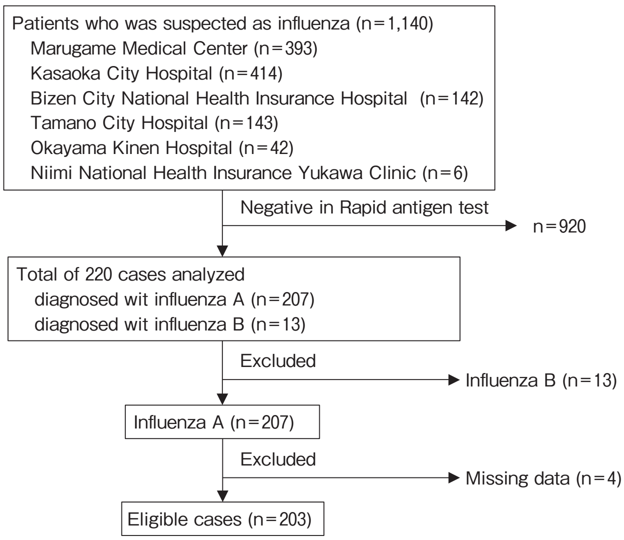

Fig. 1 Outline of the study.

Table 1 Backgrounds and clinical manifestations of the patients diagnosed with influenza type A

	Total	Younger group (20–49 years)	Middle-aged group (50–64 years)	Older group (≥65 years)	*P*-value
Total number of the cases	203	113	51	39	
(A) Background					
Age, median [IQR]	45.5 [35, 58]	37 [30, 43]	56 [52, 58]	72 [68, 77]	
Sex M/F	114/89	68/45	29/22	17/22	
Vaccination rate (%)	35.9 (66/184)	29.9 (32/107)*	27.9 (12/43)*	64.7 (22/34)*	0.001[2)]
(B) Manifestations					
Body temperature, mean ± SD					
Maximum	38.4 ± 0.9 (182)	38.5 ± 0.9 (103)	38.3 ± 0.9 (44)	38.2 ± 0.7 (35)	0.058[1)]
At first physician visit	37.7 ± 0.9 (195)	37.8 ± 0.9 (109)*	37.5 ± 1.1 (49)	37.4 ± 0.9 (37)*	0.031[1)]
Respiratory symptoms (%)					
Nasal	66.7 (134/201)	69.6 (78/112)	62.8 (32/51)	63.2 (24/38)	0.623[2)]
Pharyngeal	71.9 (146/203)	76.1 (86/113)	72.6 (37/51)	59.0 (23/39)	0.12[2)]
Lower respiratory	86.6 (175/202)	90.3 (102/113)	80.4 (41/51)	84.2 (32/38)	0.74[2)]
Systemic symptoms[†] (%)	73.7 (146/198)	80.9 (89/110)*	75.5 (37/49)*	51.3 (20/39)*	0.002[2)]
Headache (%)	63.3 (124/196)	67.6 (73/108)	60.8 (31/51)	54.1 (20/37)	0.307[2)]
Gastrointestinal symptoms[††] (%)	11.0 (22/200)	12.7 (14/110)	11.8 (6/51)	5.1 (2/39)	0.442[2)]

IQR, interquartile range; SD, standard deviation. [†]Chills, muscle, and joint pain; [††]Nausea and diarrhea.
Numbers in the parenthesis indicate the number of cases that were available. *Shows the groups in which statistical significance was observed.
[1)]Kruskal-Wallis test; [2)]Fisher's exact test.
Some data were missing because it was obtained by self-administered questionnaire.

were 37.3±0.7°C (N=20) and 37.3±1.0°C (N=12), respectively ($p=0.85$).

The correlations between age and body temperature showed that older patients were less likely to have elevated body temperatures. Spearman's correlation analysis showed inverse correlations between age and the maximum body temperature ($p=0.005$) and between age and temperature at first physician visit ($p<0.001$) (Fig. 2). That is, the older the patient, the lower the body temperature. To investigate the influence of vaccination on the body temperature, we subdivided the data into those vaccinated and those unvaccinated or unknown. For maximum body temperature, the vaccinated patients had a stronger correlation coefficient of −0.28 compared with the unvaccinated patients (correlation coefficient; −0.12), though there was no significant difference. As for the body temperature at first physician visit, the vaccinated also had a stronger correlation coefficient of −0.29 ($p=0.026$) compared with the unvaccinated (correlation coefficient; −0.17).

The respiratory tract manifestations of the study patients are shown in Table 1 as well. Nasal, pharyngeal, and lower respiratory symptoms were observed in 66.7%, 71.9%, and 86.6% of the patients, respectively. Among the three age groups, the incidences of respiratory symptoms did not show any significant differences. The different parts of the respiratory system (nasal, pharyngeal, or lower respiratory tract) where the symptoms occurred are summarized in Fig. 3. The proportions of patients in the younger, middle-aged, and older groups with no respiratory symptoms were 1.8%, 3.9%, and 7.7%, respectively. These ratios increased as the number of respiratory areas involved increased in each age group. All three areas were involved in 52.2%, 39.2%, and 41.0% of the younger, middle-aged, and older groups, respectively, indicating that older individuals tended to manifest limited respiratory symptoms.

Systemic symptoms such as chills, muscle pain, and arthralgia were reported in 80.9% and 75.5% of the patients in the younger and middle-aged groups, respectively, and these percentages were significantly higher than the percentage of patients in the older group with systemic symptoms (51.3%) ($p=0.002$). Headache and gastrointestinal symptoms were found in 63.3% and 11.0% of the patients, respectively. However, no statistical differences were found among the three age groups (Table 1).

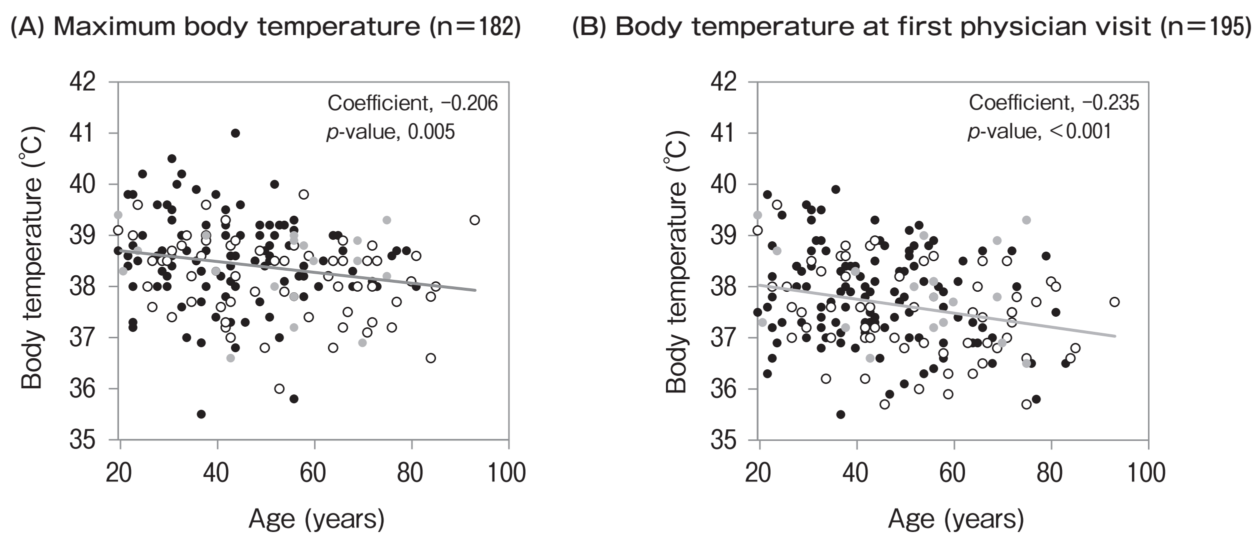

Fig. 2 Correlation between age and maximum body temperature (A) and temperature at first physician visit (B). Statistical analyses were performed using Spearman's rank correlation test. The case numbers of the vaccinated (white dots), the unvaccinated (black dots), and unknown vaccination status (gray dots) in the maximum body temperature (**A**) were 61, 103, and 18, respectively. The case numbers in the temperature at first physician visit (**B**) were 61, 115, and 19, respectively. The correlation coefficients for (i) overall, (ii) the vaccinated (white dots), and (iii) the unvaccinated (black dots) for (**A**) maximum body temperature were (i) −0.206 ($p=0.005$), (ii) −0.28 ($p=0.082$), and (iii) −0.12 ($p=0.248$). Similarly, those for (**B**) body temperature at first physician visit were (i) −0.235 ($p<0.001$), (ii) −0.29 ($p=0.026$), and (iii) −0.17 (p value, 0.069).

The time from disease onset to first physician visit is shown in Fig. 4. In the younger group, 74.5%, 17.0%, and 8.5% of the patients visited a hospital within 1 day, after 1-2 days, and after ≥3 days, respectively. In the middle-aged group, 60.0%, 28.0%, and 12.0% of the patients visited a hospital within 1 day, after 1-2 days, and after ≥3 days, respectively. In the older group, 44.1%, 26.5%, and 29.4% of the patients visited a hospital within 1 day, after 1-2 days, and after ≥3 days, respectively. These data suggest that older people tended to visit a hospital for consultation in a later phase after the disease onset.

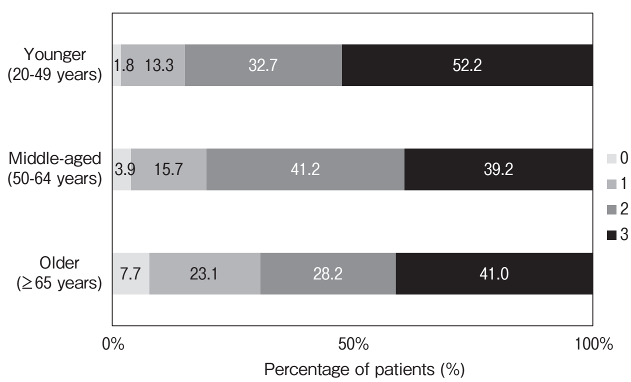

Fig. 3 The numbers of respiratory areas (nasal, pharyngeal, or lower respiratory tract) where the symptoms occurred, by age group. The number of infectious sites (horizontal axis) indicates the number of respiratory areas (either nasal, pharyngeal, or lower respiratory) where the symptoms occurred. The numbers of cases in the younger, middle-aged, and older groups were 71, 93, and 38, respectively.

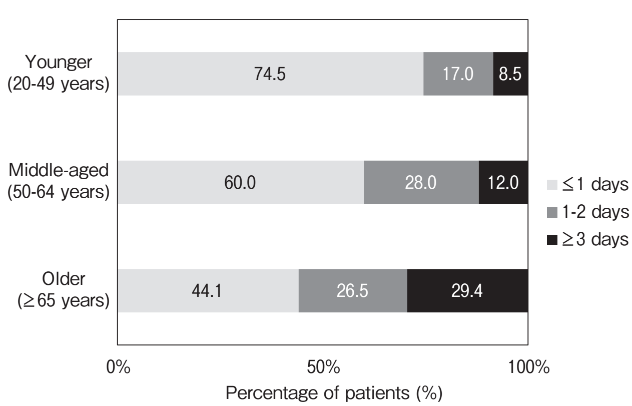

Fig. 4 Time from disease onset to first physician visit, by age group. The numbers of cases in the younger, middle-aged, and older groups were 106, 50, and 34, respectively.

Discussion

This study revealed the following three characteristics of influenza infection in the elderly compared with younger age groups: (i) the elderly were less likely to have elevated body temperatures; (ii) the elderly were less likely to have respiratory and systemic symptoms; and (iii) the elderly tended to visit a hospital comparatively later than younger individuals.

First, we found that older people appeared to experience a lower-grade fever when infected with an influenza virus. The typical presentations of patients with influenza are acute-onset high fever accompanied by systemic symptoms and a wide range of respiratory symptoms. The World Health Organization definition of influenza also lists acute-onset high fever above 38°C and cough as clinical features suggesting influenza [10]. In a previous study examining the clinical symptoms and pretest probabilities of influenza in primary care settings, the absence of cough and fever >37.8°C was reported to be useful in excluding individuals with influenza infections, although the median age of the participants in that study was relatively low (27-28 years) [11]. In general, however, as people age, they tend to be afebrile and asymptomatic when they develop an infectious disease [12]. According to a previous study from Japan, 13.6% of patients aged ≥65 years with influenza type A showed a maximum body temperature <37.5°C [8]. A similar tendency was also observed in our study, in which 17.9% of the patients aged ≥65 years had a temperature of <37.5°C. Our correlation analysis revealed that the body temperature decreased as the age of the patients progressed. From these findings, we conclude that older people infected with influenza present a lower grade fever compared with young people. However, a comparison of those with and without an influenza vaccination revealed that the inverse correlation between age and fever was stronger in the vaccinated group. The vaccination rates in our cohort were significantly higher in the elderly, and this fact could have resulted in the smaller body temperature elevation observed in the elderly.

Second, respiratory and systemic symptoms were also less likely to occur in the elderly. Patients with influenza usually experience nasal, pharyngeal, and cough symptoms; *e.g.*, according to a previous study in which 86.8% of the individuals had influenza type A, with a mean age of 34.8 years, 91%, 84%, and 93% of these patients had nasal, pharyngeal, and cough symptoms, respectively [13]. Practically, the absence of these respiratory symptoms reportedly lowers the possibility of influenza; the positive likelihood ratios of nasal congestion and cough for the diagnosis of influenza were 0.49 and 0.42, respectively [14]. Accordingly, a lack of these typical manifestations reduces the clinical implications of the disease, possibly resulting in a delay in the diagnosis. The present study showed that the elderly group tended to have fewer respiratory symptoms as well and were less likely to develop systemic symptoms than younger patients (Table 1 and Fig. 3). Lower respiratory tract symptoms tended to be present at a higher rate (84.2%) than other respiratory symptoms in the older population, suggesting that the emergence of cough or sputum may be a clue to suspect influenza in the elderly. Similarly, other studies also reported the diagnostic value of acute-onset fever accompanied by cough for the diagnosis of influenza in patients aged ≥ 60 years [14, 15]. Compared with other viral infections, influenza infection tends to involve a longer duration of fever, possibly causing systemic symptoms such as headache, muscular arthralgia, and chills more frequently [16]. A previous report concluded that the likelihood ratio of such systemic symptoms for the diagnosis of influenza was 2.6 (95% confidence interval, 2.0-3.2) in patients aged ≥ 60 years [14]. In contrast, such systemic symptoms were present in only half of the patients in the older group, indicating the difficulty of diagnosing influenza among aged individuals. Apart from the typical manifestations, it is important to focus on any decrease in activities of daily living in the elderly to increase the pre-test probability of influenza [17].

Third, our study found that the time from disease onset to first physician visit was longer in the older group. To the best of our knowledge, no recent studies have compared this time interval among patients in different age groups. We speculate that this difference may be due to various factors, including the fact that the symptoms may have been less apparent in the older group as explained above, as well as to the accessibility of hospitals and economic problems. According to a study that described a case of nosocomial influenza in an acute hospital, 32% of the patients who had a body temperature of < 38°C were diagnosed ≥ 3 days from the disease onset [18]. In contrast, patients presenting with a high fever of ≥ 38°C were diagnosed earlier. Thus, the higher the number of older patients with influenza, the higher the possibility that influenza patients can be overlooked because of their latent symptoms. As a matter of course, if a patient is diagnosed at a later point in the disease course, the risk of transmission to the surrounding population increases. Outbreaks of influenza can occur in both hospitals and nursing homes [9, 18], and healthcare workers should be aware that many older adults with influenza only exhibit nonspecific symptoms. In addition, the other factors contributing to this time delay in seeking treatment, such as hospital accessibility and economic problems among the elderly, should be addressed. In this aging Japanese society, a comprehensive administrative support system for the elderly must be established in order to increase their access to medical services.

Pathophysiological mechanisms that can explain the greater mortality rate of influenza in the elderly should be discussed. Based on a global epidemiological study, the mortality rate of people < 65 years of age (1.0-5.1/100,000) is apparently better than the rate of those aged 65-74 years (13.3-27.8/100,000) and those aged > 75 years (51.3-99.4/100,000) [19]. Generally, the immune system weakens as humans age due to declines in humoral-, and cell-mediated immunities. In particular, the cell-mediated immunity that is dependent on the balance between the subsets of helper T cells (Th1 as pro-inflammatory and Th2 as anti-inflammatory) is weakened with aging, resulting in infectious diseases affecting the elderly with greater severity [20]. In addition, reduced reactivity to specific pathogens is observed in the elderly as a result of the T cells in the thymus, spleen, and lymph nodes having less maturation capacity in older individuals [21]. Dysregulation of the cytokine network as a geriatric phenomenon is also responsible for the deterioration of the response of innate and adaptive immune mechanisms. It is known that a lower ratio of interferon-γ to interleukin-10 and lower levels of inducible granzyme B activity in the elderly are associated with high influenza mortality [22]. In addition to the molecular mechanisms, aging can lead to physical weakness in the elderly, with a reduced mucociliary clearance and decreased cough reflex resulting from sarcopenia [23]. All of these geriatric changes are potential contributing factors to the severity of influenza in the elderly.

There are some limitations to this study. First, antigen tests, but not polymerase chain reaction (PCR) tests, were conducted to diagnose influenza in this study. Generally, the sensitivity of the rapid antigen test is reported to be lower than that of the PCR tests [24], and the cases could have been underdiagnosed. Second, the clinical data were obtained using self-administered questionnaires, for which there could potentially be a recall bias. Third, it was not determined whether or not the patients took any medications to ameliorate the symptoms before the consultation. Fourth, although the study aimed to examine the differences in clinical symptoms between younger and older populations, only 39 individuals aged ≥ 65 years were eligible for the study. This could be attributed to the fact that the study was performed amid the coronavirus disease 2019 (COVID-19) pandemic in Japan, and the influenza epidemic in this period might have differed from the epidemics reported in previous years. We assume that older people refrained from going outside during the study period, which may have led to a delay or avoidance of hospital visits. Fifth, the vaccination rates were different among the age groups (higher in older people), which could have influenced the clinical manifestations because the vaccine effectively reduced the severity of the condition and prevented the disease from becoming severe [25]. Finally, some patients might have visited other outpatient clinics before visiting our facilities, but this was not investigated in the questionnaire survey.

In summary, our study found that clinical manifestations, including fever, respiratory, and systemic symptoms, in older patients infected with influenza were less apparent compared with those in younger individuals. In addition, the time from disease onset to first physician visit tended to be longer in older patients. These characteristics of influenza in the elderly may result in a delayed diagnosis in the aged population, possibly causing delays in treatment and thus the development of secondary complications. From the perspective of infection prevention, the latent manifestation of influenza among the elderly increases the risk of the rapid spread of the infection among elderly individuals, such as those in nursing homes and chronic care facilities. During the influenza epidemic season, even in the absence of fever and respiratory symptoms, clinicians should suspect influenza with a low threshold of doubt in elderly patients and should proactively perform a specific test to diagnose the infection in order to provide early treatment and prevent further epidemics in the older population. Patients with COVID-19 can also be asymptomatic; hence, diagnoses of viral diseases must be established without relying solely on the patient's clinical manifestations. General practitioners should further inform the public, especially elderly people, of the importance of seeing a doctor without a delay when they feel that their condition is unusual, even in the absence of typical manifestations.

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