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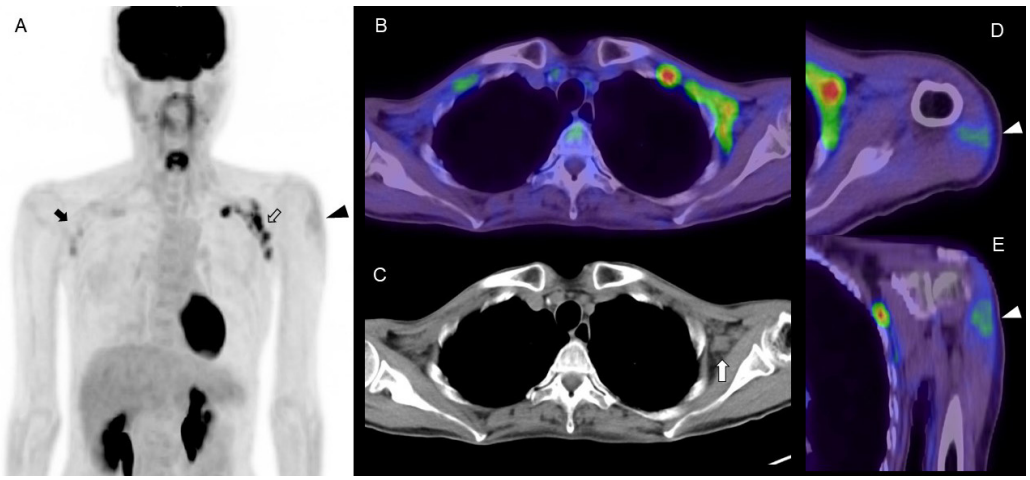

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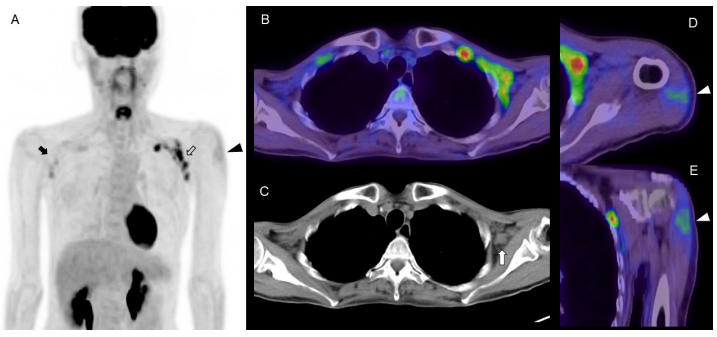

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Behavioral changes adopted to constrain COVID-19 in Japan: What are the implications for seasonal influenza prevention and control?

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Abstract: Respiratory disease deaths associated with seasonal influenza are estimated to be 290,000 to 650,000 per year globally. In Japan, seasonal influenza affects more than 10 million people per year, and especially children, the elderly, and patients with underlying medical conditions, and seasonal influenza can cause severe illness. As SARS-CoV-2 continues to spread, the combined risk of concurrent influenza epidemics and the COVID-19 pandemic are a concern. When the status of influenza virus infections during the 2020-2021 flu season was compared to the 2011 to 2020 flu seasons, data indicated the absence of seasonal influenza outbreaks in Japan during the COVID-19 pandemic. The number of flu patients was roughly estimated to be 14,000 nationwide from September 2020 to March 2021, which marks the first sharp decrease since national influenza surveillance started in 1987 in conjunction with National Epidemiological Surveillance of Infectious Diseases (NESID). Moreover, approximately 500 sentinel sites (designated medical facilities) nationwide reported only 112 patients with severe influenza who required hospitalization. Since prevention and control measures amidst the COVID-19 pandemic have become the "new normal", one can reasonably assume that the absence of a seasonal influenza outbreak is related to prevention and control measures implemented in response to the COVID-19 pandemic. Basic infection prevention measures were thoroughly implemented, such as wearing masks, handwashing, and avoiding confined spaces, crowded places, and close-contact settings. More importantly, the behavioral changes adopted to constrain COVID-19 during three declared states of emergency reduced population density and contact with people, including closing schools, asking restaurants to reduce their business hours, teleworking, curbing the flow of people during vacation week, *etc*. These behavioral changes will serve as a valuable reference to reduce the spread of seasonal influenza in the future.

***Keywords*:** COVID-19, influenza, new normal, behavioral pattern, Japan

Introduction

Seasonal influenza is an acute respiratory illness mainly caused by influenza virus types A or B. Annual influenza epidemics result in substantial mortality, especially among adults aged 65 years and older. Globally, an estimated 291,243–645,832 influenza-associated respiratory deaths (4.0–8.8 per 100,000 individuals) occurred annually from 1999-2015 (*1*).

In Japan, seasonal influenza affects more than 10 million people each year, and especially children, the elderly, and patients with underlying medical conditions, and seasons influenza can cause severe illness (*2-4*). As SARS-CoV-2 continues to spread, the combined risk of concurrent influenza epidemics and the COVID-19 pandemic are a concern (*5*).

Seasonal influenza in Japan during the 2011-2021 flu season

Effective surveillance and monitoring of influenza outbreaks are critical to evaluating the impact of the disease on the community and to devising disease management policies. In Japan, the major national influenza surveillance systems include nationwide sentinel-based surveillance of influenza-like illness (based on 5,000 sentinel sites), virological surveillance (based on 500 designated sentinel sites), influenza-associated hospitalizations (based on 500 designated sentinel sites), surveillance of student absences and school closures, and national epidemiological surveillance of vaccine-preventable diseases (NESVPD).

In 1999, Japan established a system of 5,000 influenza surveillance sentinel sites (60% pediatrics and 40% internal or general medicine clinics) throughout the country; the number of patients is estimated nationwide on a weekly basis starting in September, when flu season commences (*6*). During the 2020-2021 flu season (from September 2020 to March 2021), the estimated number

of flu patients was roughly 14,000 nationwide, based on reports from sentinel sites (*7*). Moreover, approximately 500 sentinel sites (designated medical facilities) nationwide reported only 112 patients with severe influenza who required hospitalization (*8*).

In comparison to influenza virus infections during the previous flu seasons from 2011 to 2020 (Figure 1), data indicated the absence of seasonal influenza outbreaks during the 2020-2021 flu season in Japan amidst the COVID-19 pandemic. In addition, outbreaks of seasonal influenza did not occur, so weekly reports stopped after Week 9 (March 1-7) of 2021 (*7,9*). Seasonal influenza previously affected more than 10 million people per year in Japan, but there has been an absence of outbreaks and a sharp decrease in flu patients during the 2020-2021 flu season. This marks the first time such a situation has occurred since national influenza surveillance started in 1987 in conjunction with National Epidemiological Surveillance of Infectious Diseases (NESID).

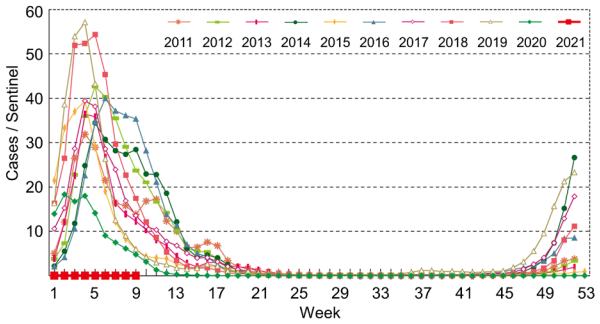

Figure 1. The number of flu patients according to reports from influenza sentinel sites during the 2011-2021 flu seasons in Japan. Data Source: *https://www.niid.go.jp/niid/ja/data.html*

What are the reasons for the absence of seasonal influenza outbreaks during the COVID-19 pandemic?

What are the reasons for the absence of seasonal influenza outbreaks during the 2020-2021 flu season in Japan amidst the COVID-19 pandemic? One can reasonably assume that the lack of such outbreaks is related to the prevention and control measures implemented in response to the COVID-19 pandemic. In addition to guaranteed medical care and tightened border controls (*10-12*), behavioral changes adopted to constrain COVID-19 are an essential approach to reducing the risk of disease transmission (*13-16*). Table 1 summarizes the government's prevention and control measures calling for behavioral changes among the general public during the

Table 1. The Government's prevention and control measures calling for behavioral changes among the general public during the three declared states of emergency in Japan

State of Emergency	First state of emergency (April 7 to May 25, 2020)	Second state of emergency (January 8 to March 21, 2021)	Third state of emergency (April 25 to June 20, 2021)
Purpose	Reduce contact with other people by at least 70%, or 80% if possible	Strategy targeting restaurants	Reduce the flow of people during vacation week
Regions	All prefectures	11 prefectures (Tokyo, Saitama, Chiba, Kanagawa, Tochigi, Gifu, Aichi, Kyoto, Osaka, Hyogo, and Fukuoka)	10 prefectures (Tokyo, Hokkaido, Aichi, Kyoto, Osaka, Hyogo, Okayama, Hiroshima, Fukuoka, and Okinawa)**
Schools	School closures*	Open	Open (restrictions on after-school club activities)
Events	Cancellation	Event requirements (maximum number of people, capacity, no food or drink, *etc.*)	Reduce the capacity of the venue by 50% or more to a maximum of 5,000 people. Open until 9 PM
Restaurants	Reduced business hours (until 8 PM at the latest), alcohol served until 7 PM in Tokyo, *etc.*	Reduced business hours (until 8 PM at the latest) and alcohol served until 7 PM	Restaurants and bars that serve alcoholic beverages and offer karaoke were requested to suspend operations while other restaurants were asked to remain open no later than 8 PM
Businesses	Promotion of teleworking	Thorough implementation of teleworking (on-site employees reduced by 70%)	Thorough implementation of teleworking (status of implementation was asked to be disclosed)
Commercial facilities	Department stores, theaters, pachinko parlors, *etc.* were asked to suspend operations	Reduced business hours (until 8 PM)	Department stores, theaters, pachinko parlors, *etc.* were asked to suspend operations. After May 12, reduced business hours (until 8 PM)
Penalty	No	Amended legislation stipulates a fine of up to 300,000 yen	A fine of up to 300,000 yen
Transit/travel	Stay home as much as possible	Stay home, thoroughly implemented after 8 PM in particular; Public asked to refrain from traveling between prefectures	Stay home, thoroughly implemented after 8 PM in particular. Public asked to refrain from traveling between prefectures.

Data Source: *https://corona.go.jp/emergency.* *School closures starting 2 March, 2020 (*https://www.mext.go.jp/content/202002228-mxt_kouhou01-000004520_1.pdf*); **Pre-emergency measures were also implemented by 5 other prefectures.

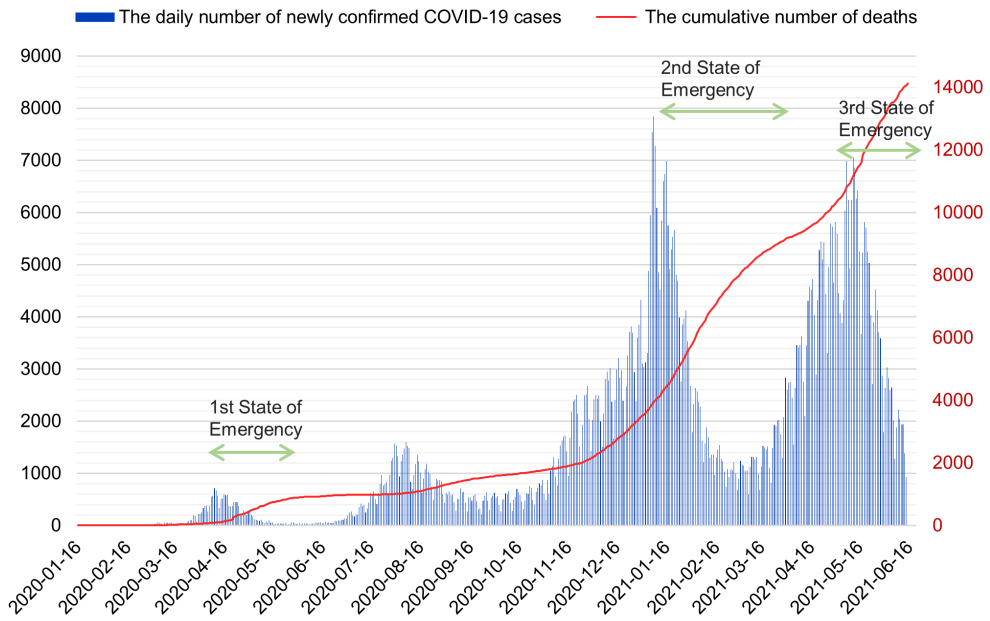

Figure 2. The daily number of newly confirmed COVID-19 cases and the cumulative number of deaths from January 2020 to June 2021 in Japan. Data Source: *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000164708_00001.html*

three declared states of emergency in Japan.

Japan's first case of COVID-19 was reported on January 16, 2020 (*17*). A first state of emergency was subsequently declared from April 7 to May 25, 2020 (Weeks 15 to 22) (*18*). The Government set a goal of reducing human contact by at least 70% and by 80% if possible, and some places where people gather, such as schools and public facilities, were closed, events were canceled, and the general public was asked to stay home as much as possible.

A second state of emergency was declared from January 8 to March 21, 2021 (Weeks 1 to 11) in 11 prefectures (Tokyo, Saitama, Chiba, Kanagawa, Tochigi, Gifu, Aichi, Kyoto, Osaka, Hyogo, and Fukuoka) (*19*). Measures targeting restaurants were implemented. Restaurants were allowed to be open until 8 PM at the latest, alcohol could be served until 7 PM, and a fine of up to 300,000 yen could be imposed on those restaurants that failed to comply. Moreover, businesses were asked to thoroughly implement teleworking in order to reduce the number of on-site employees by 70%.

A third state of emergency was declared from April 25 to June 20, 2021 (Weeks 16 to 24) in 10 prefectures (Hokkaido, Tokyo, Aichi, Kyoto, Osaka, Hyogo, Okayama, Hiroshima, Fukuoka, and Okinawa) (*20*). The goal was to control the flow of people during the vacation week for a brief period of time. Restaurants and bars that serve alcoholic beverages and offer karaoke were asked to suspend operations while other restaurants were asked to remain open no later than 8 PM. Teleworking was asked to be implemented and status of implementation was asked to be disclosed. Although schools remained open to an extent, after-school club activities were restricted to a degree.

Figure 2 shows the daily number of newly confirmed COVID-19 cases from January 2020 to June 2021. During the period from when the first patient was reported on January 16, 2020 to the end of the third state of emergency on June 20, 2021, the number of confirmed cases increased to 784,000 and 14,400 people have unfortunately died (*21*). The number of confirmed cases decreased during all three declared states of emergency.

Behavioral changes for prevention and control of seasonal influenza in the future: What has been learned?

Prevention and control measures implemented in response to COVID-19 have become the "new normal" in daily life and work, and they seem to have been effective in reducing the spread of seasonal influenza as well. Basic infection prevention measures have been thoroughly implemented, such as wearing masks, handwashing, and avoiding confined spaces, crowded places, and close-contact settings. More importantly, the behavioral changes adopted to constrain COVID-19 during three declared states of emergency reduced population density and contact with others, including closing schools, asking restaurants to reduce their business hours, teleworking, curbing the flow of people during vacation week, *etc*.

One can reasonably assume that the absence of seasonal influenza outbreaks during the 2020-2021 flu season in Japan is related to the prevention and control measures implemented in response to the COVID-19 pandemic. Behavioral changes adopted to constrain COVID-19 will serve as a valuable reference to reduce the spread of seasonal influenza in the future.

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Effects of COVID-19 vaccination on FDG-PET/CT imaging: A literature review

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Abstract: COVID-19 vaccination using mRNA technology began at the end of 2020 in several countries, approximately 9 months after the WHO declared the new coronavirus a pandemic, and began in Japan at the end of February 2021. Several studies have reported FDG avidity in enlarged axillary lymph nodes as a specific feature of FDG-PET/CT imaging after COVID-19 vaccination. A major concern is that this finding could lead to a misdiagnosis in patients with various types of malignancy. We review the impact of COVID-19 vaccination on the management of patients scheduled for FDG-PET/CT in the setting of nationwide mass vaccination.

***Keywords*:** COVID-19, FDG, PET/CT, vaccine

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2, has affected many countries worldwide (*1*). As of 10 June 2021, a total of 174,488,358 cases and 3,759,138 deaths have been reported (*2*). The development of COVID-19 vaccines has played a key role in protecting people from COVID-19 (*3*), as shown by the substantial early reductions in SARS-CoV-2 infection and symptomatic COVID-19 rates recorded following administration of the first dose of the vaccine (*4*). In general, vaccine development takes approximately 15 years (*5-6*), therefore the speed of development of COVID-19 vaccine within one year, and the proven efficacy of vaccines against SARS-CoV-2 are undoubtedly scientific breakthroughs. The two major mRNA-based vaccines, produced by Moderna and Pfizer/BioNTech, are 94-95% effective and there have been no critical safety concerns to date (*7,8*).

[^{18}F]-2-fluoro-2-deoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) is useful for accurate tumor staging in various types of cancer and for monitoring the response to cancer therapy. Accurate nodal staging is one of the advantages of FDG-PET/CT, and is recommended for this purpose in several clinical guidelines. In contrast, nonspecific or inflammatory-related FDG uptake in the lymph nodes has been a limitation of FDG-PET/CT (*9*). We have previously reported the FDG-PET/CT findings of patients with COVID-19 as increased FDG uptake in lung lesions with segmental ground-glass densities and plaques, in normal-sized or slightly enlarged lymph nodes, and in the bone marrow and spleen (*10*).

Several recent reports have announced the specific findings of intense FDG uptake in axillary, supraclavicular and cervical lymph nodes on FDG-PET/CT following COVID-19 vaccination based on mRNA biotechnology. Since lymphadenopathy after vaccination has been reported with several other types of available vaccines (*11-13*), the FDG-PET/CT imaging feature following COVID-19 vaccination could be predictable. However, the impact of the FDG-PET/CT following COVID-19 vaccination was higher than we had expected. Therefore, we present here the features of FDG-PET/CT imaging and conduct a review of the literature regarding the management of patients who underwent FDG-PET/CT after COVID-19 vaccination.

Incidence of lymph node swelling in patient with COVID-19 infection

Among patients with COVID-19 infection, lymph node enlargement is seen on CT in less than 1% (*14*). These lymph nodes are generally small, nonspecific, and regular in shape. Enlargement of the lymph nodes is not significant, and FDG uptake in mediastinal and supraclavicular lymph nodes is frequently seen in patients with COVID-19 (*10*). Swelling of lymph nodes indicates immunoreactions that are activated by inflammatory cells. In the immune response to viral infections, the number of monocytes in lymphoid tissue increases, leading to increased FDG uptake (*15*).

However, several studies in patients with COVID-19 have reported negative FDG uptake in mediastinal and

supraclavicular lymph nodes which may occur in the minimally invasive and early stages of the disease (*16*). Therefore, the immune response is weak or almost absent in the early stage of the disease and becomes more active over time. In addition, the reduction of FDG uptake in lymph nodes may indicate normalization of a hyperactive immune response in the body.

Incidence of lymph node swelling following COVID-19 vaccination

A public notification from the Centers for Disease Control and Prevention (CDC) indicated that the incidence of lymphadenopathy after the Pfizer-BioNTech COVID-19 vaccination was imbalanced, with 58 more cases recorded in a vaccine group (n = 64) compared with a placebo group (n = 6). Lymphadenopathy occurred in the arm and neck regions and was reported within 2-4 days after vaccination. The average duration of lymphadenopathy was approximately 10 days. However, lymph node swelling was defined as an unsolicited adverse event in this clinical trial (*17*). It appears that the size and number of lymphadenopathy was relatively severe as being able to identify with palpation and/or visual inspection. In a Moderna clinical trial with a cohort aged 18-64 years, axillary swelling or tenderness was regarded as a solicited adverse event that occurred in 11.6% of patients after the first vaccination and 16.0% after the second vaccination, which was higher than the incidence in placebos (5.0% and 4.3%, respectively) (*17*). This reaction was less common in subjects aged ≥ 65 years, occurring in 8.4% of this group after the second dose (*8,17*). These two mRNA vaccines appear to stimulate immune activity to a greater degree than do than vaccines based on traditional biotechnologies (*18*).

Features of FDG-PET/CT imaging after COVID-19 vaccination

After vaccination, lymph node size varies from normal to moderately increased with thickening of the cortex and fatty hilum, suggesting benign lesions. However, lymph nodes can show abnormal size and loss of fatty hilum shortly after vaccination, which could be considered to indicate malignancy. Therefore, it is important to carefully manage the timing of FDG-PET/CT examination with respect to the date of vaccination. FDG uptake has been identified in normal-sized to moderately enlarged axillary supraclavicular and cervical area nodes following intramuscular vaccination in the ipsilateral deltoid (*19-32*) (Figure 1). Nodal FDG uptake tends to occur within 7 days of vaccination and generally disappears by 12-14 days (*12*). However, it can remain for 4-6 weeks (*19*) or 7-10 weeks (*23*) after the injection. Lymph nodes on the injected side are mostly affected, but contralateral lymph nodes can also show FDG uptake. Therefore, the FDG-PET/CT findings can lead to misdiagnosis in the evaluation of malignancy and inflammatory disease, particularly with regard to breast cancer, melanoma, lymphoma, and sarcoidosis (*31*).

Cohen *et al.* categorized vaccine-associated hypermetabolic lymphadenopathy (VAHL) according to the intensity and area of FDG uptake in axial lymph nodes as follows: grade 1, mild FDG-uptake intensity ($SUV_{max} < 2.2$); grade 2, moderate FDG-uptake intensity ($2.2 \leq SUV_{max} < 4$); grade 3, high FDG-uptake intensity ($SUV_{max} \geq 4$) in normal-size nodes; and grade 4, high FDG-uptake intensity ($SUV_{max} \geq 4$) in enlarged nodes. The incidence of VAHL was 36.5% among all subjects who were vaccinated, but was significantly higher after the 2nd vaccination (45.8%)

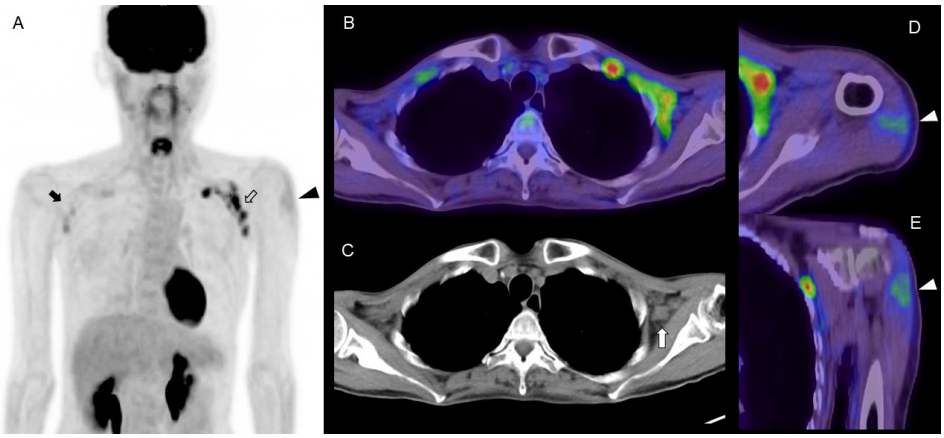

Figure 1. FDG PET/CT images in a woman in her 50s with abdominal malignancy at 4 days after COVID-19 vaccination. **(A)** MIP image, **(B)** axial fusion image, **(C)** CT image, **(D)** axial fusion image of deltoid muscle, **(E)** coronal fusion image of deltoid muscle. Increased FDG uptake is seen in the left axilla with supraclavicular lymphadenopathy (open arrow). There is slight FDG uptake in the right axillary and supraclavicular areas (arrow). The CT image shows enlarged lymph nodes with loss of fatty hilum in the left axillary and supraclavicular areas (white arrow). Intense FDG uptake in the left deltoid muscle indicates the site of COVID-19 vaccine injection (arrowhead). FDG uptake in the spleen was almost equal to that in the liver, which might have been caused by the vaccination.

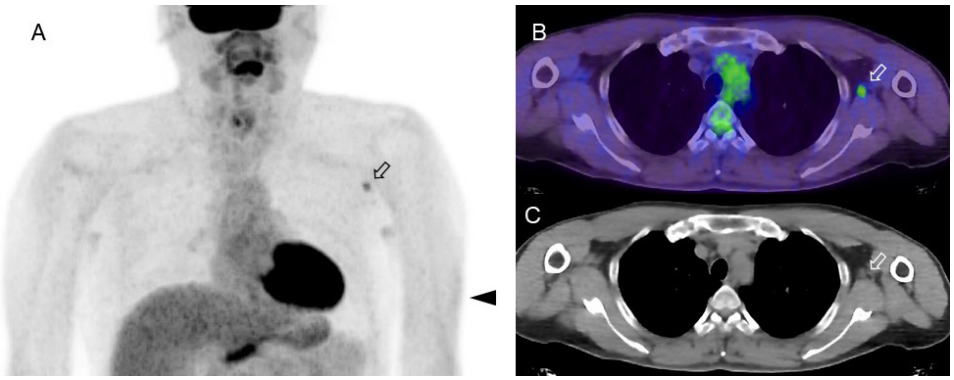

Figure 2. FDG-PET/CT images in a subject who received an influenza vaccination 4 days before the imaging examination. (A) MIP image, **(B)** axial fusion image, **(C)** CT image. Focal FDG uptake is seen in an axillary lymph node, which was slightly enlarged on CT image. Slight FDG uptake in the left arm indicates the site of COVID-19 vaccine injection at subcutaneous tissue (arrowhead). There are slight and symmetrical FDG uptake in the bilateral axillary area due to non-specific uptake for sweat glands.

compared with the 1st vaccination (26.3%). Node size, FDG uptake in axial lymph nodes beyond level 1, and the site of vaccination were all more prominent after the 2nd vaccination. After the first vaccination, the incidence of VAHL was higher at 6-12 days after vaccination compared with that in the first 5 days and at 13 days. After the second vaccination, the incidence and grade of VAHL were highest in the first 6 days, decreased gradually over time, and were significantly low at more than 20 days after vaccination. VAHL was recognized in 29% of vaccinated patients at 3 weeks after the second vaccination, but only 7% had grade 3 or 4 VAHL. After the first vaccination, there was a higher incidence and higher grade of VAHL in subjects aged ≤ 62 years than in others; whereas after the second vaccination, there was a higher incidence and higher grade of VAHL in subjects aged ≤ 64 years than in others (*26*). Regarding FDG uptake in lymph nodes, greater uptake was associated with second vaccination; in contrast, lower uptake was associated with older age, immunosuppressive treatment, and hematologic disease (*30*). The incidences of FDG uptake in lymph nodes were reported as higher for the Moderna vaccine than the Pfizer vaccine (*32*).

FDG uptake in small axillary lymph nodes is a common feature after vaccination against influenza (*11-13,16,33*) and other diseases (*34*). Considering that the reaction to the COVID-19 vaccine is more severe and of longer duration than that to the influenza vaccine, the FDG-PET/CT imaging findings may represent the nature of mRNA biotechnology vaccines for increased immunogenicity compared with traditional vaccines.

Intramuscular injection into the deltoid muscle has been recommended for administration of the COVID-19 vaccine (*35*), and it has been reported that the injected muscle shows increased FDG uptake shortly after injection. The factor of occurring increased FDG uptake in the deltoid muscle following COVID-19 mRNA vaccination was the number of days between the last vaccination and second vaccination (*30*).

In Japan, the influenza vaccine is injected into subcutaneous tissue, most commonly in the upper arm. In our experience, the site of influenza injection can be confirmed as a relatively small and slight FDG uptake shortly after administration of the vaccine (Figure 2). In contrast, following administration of the COVID-19 vaccine, moderate FDG uptake is confirmed as a broad area indicating a high degree of inflammatory change in the deltoid muscle. However, it is unclear whether this uptake is related to pain and swelling at the injection site.

Increased FDG uptake can also be observed in the spleen after COVID-19 vaccination (*25*); although not mentioned specifically by the author, this finding could be observed in several of the FDG-PET/CT images in that study. In addition to FDG imaging, specific PET uptake has also been observed in ^{68}Ga-DOTA-TATE, ^{11}C- and ^{18}F-choline imaging (*30,36,37*), but less frequently with ^{68}Ga- and ^{18}F-PSMA (*41*).

Brewer *et al.* proposed lymph node swelling as a potential biomarker for successful vaccination in the DepoVax-based COVID-19 vaccine (*38*). However, further observation is necessary to clarify the relation between the antibody production and incidence of FDG-uptake after the COVID-19 vaccination.

Patient scheduling for FDG-PET/CT after COVID-19 vaccination

Physicians should take into account the specific imaging features of FDG-PET/CT and other imaging examinations following COVID-19 vaccination. When imaging studies are planned for the management of patients with COVID-19, information regarding the timing of COVID-19 vaccinations should be available for these patients. A preliminary patient interview by imaging unit staff regarding prior vaccination may be an effective method for ensuring that examinations are scheduled appropriately. Sharing this information with the radiologist would contribute to increasing the

accuracy of diagnosis.

To reduce false positive findings, FDG-PET/CT imaging should ideally be scheduled for either immediately after or 4-6 weeks after vaccination. However, immediately after vaccination, patient may request to reschedule the FDG-PET/CT test due to the common side effects (fever, nausea, chills, headache, tiredness, *etc*.) after getting a COVID-19 vaccine. Enlarged lymph nodes that are observed in the axillary, supraclavicular, or cervical areas with laterality can confuse the diagnosis (particularly in breast cancer, melanoma, lymphoma and any malignancy which have high possibility of invasion around these sites). Therefore, the vaccine should preferably be administered in the contralateral arm to the side of disease.

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Epidemiology of cardiovascular disease and its risk factors in Korea

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Abstract: Cardiovascular disease (CVD) is the leading cause of death and a major contributor to disability worldwide. Currently, Korea is among countries with the lowest CVD mortality rates, and the age-adjusted CVD mortality rate is still decreasing. However, depending on the CVD type, the mortality and incidence trends vary. Without age-standardization, cerebrovascular disease mortality peaked in 1994 (82.1 per 100K) and continued to decline until 2018 (44.7 per 100K), while heart disease mortality recorded the lowest level in 2001 (44.9 per 100K) then increased again until 2018 (74.5 per 100K). Age-standardized mortality rates showed different trends: both cerebrovascular disease and heart disease mortality rates have declined over the past few decades, although the rate of decline varies. Based on the National Health Insurance claim database, the numbers of hospitalization for cerebrovascular disease and ischemic heart disease are increasing, but the age-standardized hospitalization rates are decreasing. Unlike other types of CVDs, heart failure is rapidly increasing in both mortality and hospitalization rates regardless of age-standardization. Seventy percent of Korean adults have at least one risk factor, 41% have ≥ 2 risk factors, and 19% have ≥ 3 risk factors including hypertension, diabetes, hypercholesterolemia, obesity, and smoking. Exposure to multiple risk factors increases with age, with 65% of senior citizens over 70 having ≥ 2 risk factors and 34% having ≥ 3 risk factors. As the elderly population, especially those with multiple risk factors and chronic disorders, is increasing, the management of this high-risk group will be an important challenge to prevent CVD in Korea.

***Keywords*:** cardiovascular disease, risk factor, epidemiology, mortality, incidence, Korea

Introduction

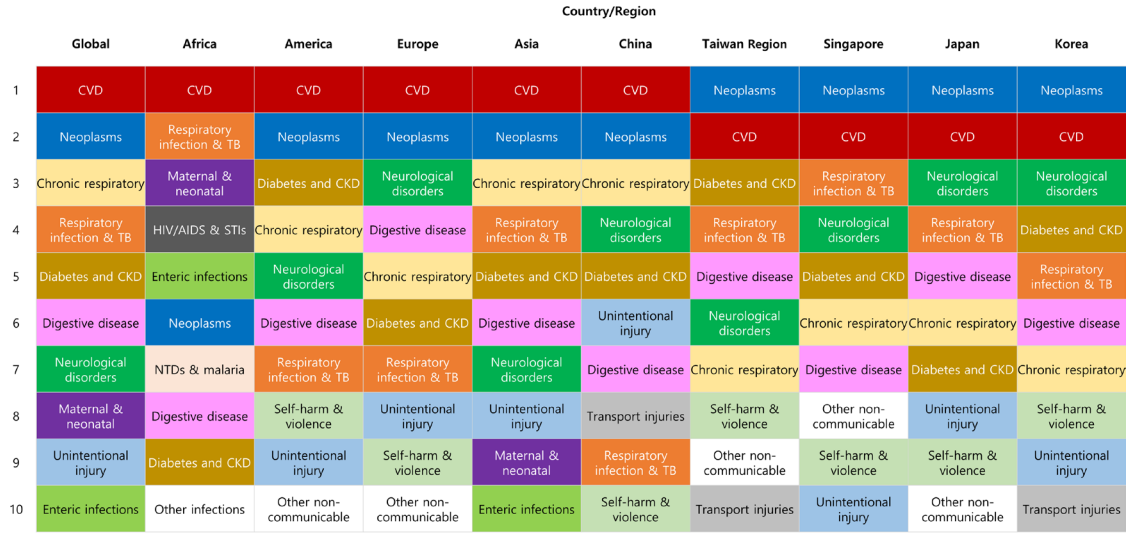
Cardiovascular disease (CVD) is the leading cause of death and a major contributor to disability worldwide (*1*). In high-income countries such as Europe, North America, and Australia, CVD mortality, mainly due to ischemic heart disease and stroke, has been decreasing since the late 20th century, and the trend of decline will continue although the rate of decline has been slowing recently. However, the prevalence of CVD will increase due to the prolonged survival of CVD patients, and the absolute number of CVD deaths will increase too because the population is aging. Assuming that the level of major cardiovascular risk factors remains unchanged, the number of middle-aged people suffering from heart disease or stroke will increase significantly in most countries, and a huge number of adults aged 35 to 64 will die of CVD over the next 30 years (*1-3*).

In South Korea (hereinafter referred to as Korea), the incidence and mortality rate of CVD have increased for decades, but the age-standardized mortality rate has recently begun to decline. However, the burden of CVD is still likely to increase. This review will look over the recent changes of CVD in Korea through descriptive epidemiologic measures such as mortality, incidence and prevalence, and predict the burden of CVD in the future through the distribution of major cardiovascular risk factors.

Deaths from CVD

An estimated 17.9 million of people died from CVDs in 2016 worldwide, representing 31% of all global deaths. Of these deaths, 85% are due to ischemic heart disease and cerebrovascular disease (*4*). Recently, CVD mortality rates are decreasing in developed countries with high income levels, but the global number of CVD deaths is expected to continue to increase as CVD is rapidly increasing in low-income and middle-income countries (*5*). CVD is the leading cause of death in most parts of the world, but it is the second leading cause of death following cancer in some regions of East Asia including Taiwan, Singapore, Japan and Korea (Figure 1) (*6*).

In Korea, CVD had been the most common cause of death until 1999, but thereafter cancer has been the number one cause of death and CVD has been the second one. Currently, Korea is among the countries showing the fastest decline in age-adjusted CVD



	Country/Region									
	Global	Africa	America	Europe	Asia	China	Taiwan Region	Singapore	Japan	Korea
1	CVD	CVD	CVD	CVD	CVD	CVD	Neoplasms	Neoplasms	Neoplasms	Neoplasms
2	Neoplasms	Respiratory infection & TB	Neoplasms	Neoplasms	Neoplasms	Neoplasms	CVD	CVD	CVD	CVD
3	Chronic respiratory	Maternal & neonatal	Diabetes and CKD	Neurological disorders	Chronic respiratory	Chronic respiratory	Diabetes and CKD	Respiratory infection & TB	Neurological disorders	Neurological disorders
4	Respiratory infection & TB	HIV/AIDS & STIs	Chronic respiratory	Digestive disease	Respiratory infection & TB	Neurological disorders	Respiratory infection & TB	Neurological disorders	Respiratory infection & TB	Diabetes and CKD
5	Diabetes and CKD	Enteric infections	Neurological disorders	Chronic respiratory	Diabetes and CKD	Diabetes and CKD	Digestive disease	Diabetes and CKD	Digestive disease	Respiratory infection & TB
6	Digestive disease	Neoplasms	Digestive disease	Diabetes and CKD	Digestive disease	Unintentional injury	Neurological disorders	Chronic respiratory	Chronic respiratory	Digestive disease
7	Neurological disorders	NTDs & malaria	Respiratory infection & TB	Respiratory infection & TB	Neurological disorders	Digestive disease	Chronic respiratory	Digestive disease	Diabetes and CKD	Chronic respiratory
8	Maternal & neonatal	Digestive disease	Self-harm & violence	Unintentional injury	Unintentional injury	Transport injuries	Self-harm & violence	Other non-communicable	Unintentional injury	Self-harm & violence
9	Unintentional injury	Diabetes and CKD	Unintentional injury	Self-harm & violence	Maternal & neonatal	Respiratory infection & TB	Other non-communicable	Self-harm & violence	Self-harm & violence	Unintentional injury
10	Enteric infections	Other infections	Other non-communicable	Other non-communicable	Enteric infections	Self-harm & violence	Transport injuries	Unintentional injury	Other non-communicable	Transport injuries

Figure 1. Leading causes of death in selected regions from the Global Burden of Disease Study. CVD, cardiovascular disease; TB, tuberculosis; CKD, chronic kidney disease; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; STIs, sexually transmitted infections; NTDs, neglected tropical diseases. (Data source: *http://www.healthdata.org/gbd/data-visualizations).*

mortality worldwide (*7*). Based on year 1983 to 2018 data on causes of death from the National Statistical Office, mortality from any circulatory system disease has decreased from 165.9 (per 100,000 population) in 1983 to 109.2 (per 100,000 population) in 2009, but increased again up to 122.7 (per 100,000 population) in 2018.

Fortunately, the death rate of cerebrovascular disease peaked at 82.1 (per 100,000 population) in 1994 and continued to decline to 44.7 (per 100,000 population) in 2018. The mortality rate from total heart diseases decreased from 95.3 (per 100,000 population) in 1983 to 44.9 (per 100,000 population) in 2001, but increased again to 74.5 (per 100,000 population) in 2018. The increase in total heart disease mortality in the early 2000s was mainly due to an increase in ischemic heart disease mortality, and the increase in the 2010s was largely due to an increase in heart failure mortality (Figure 2). The recent rapid increase in heart failure mortality in Korea is attributed to a surge in the elderly population, an increasing number of survivors after coronary artery disease, and an increase in heart failure diagnosis rates.

Figure 3 shows the age-standardized mortality from total heart diseases, ischemic heart disease, heart failure and cerebrovascular diseases in Korean men and women. Age-standardized rates were calculated using the direct method with the age structure of each male and female population in 2018. Over the past 36 years, the age-standardized mortality rate from total heart disease decreased a lot both in men and women. In the past, heart disease mortality rates were much higher in men than women, but have been reversed recently. The reason why heart disease mortality is higher in women is because the proportion of elderly people is much higher in women. When both men and women's heart disease mortality rates are standardized to the same population structure, the rate is still higher in men than in women (*8*). Age-standardized mortality rate from ischemic heart disease increased rapidly until the mid-2000s. In men, it peaked at 56.2 (per 100,000 population) in 2002, and in women at 50.4 (per 100,000 population) in 2006. However, it began to decline from that point to 2018, with a decrease of 45% for men and 49% for women. On the other hand, the age-standardized mortality from heart failure is increasing rapidly, which has led to a slowdown in the rate of decline in heart disease mortality. Heart failure mortality is increasing much faster in women because the proportion of elderly women is increasing faster.

For stroke (cerebrovascular disease), the crude mortality rate also decreased, but the age-standardized mortality rate decreased much faster. Between 1983 and 2018, the age-standardized stroke mortality decreased by 83% in men and 76% in women. Among the subtypes of stroke, there had been more deaths caused by hemorrhagic stroke (non-traumatic intracerebral hemorrhage and subclinical hemorrhage) until 2002, but there were more deaths caused by ischemic stroke since then. Both because of the decreasing incidence of stroke due to improved blood pressure control since the 1990s and the improving survival of patients with acute stroke might contribute to the rapid reduction of stroke mortality in Korea.

Incidence and prevalence of CVD

Unlike mortality data, national representative morbidity data are very limited, making it difficult to estimate

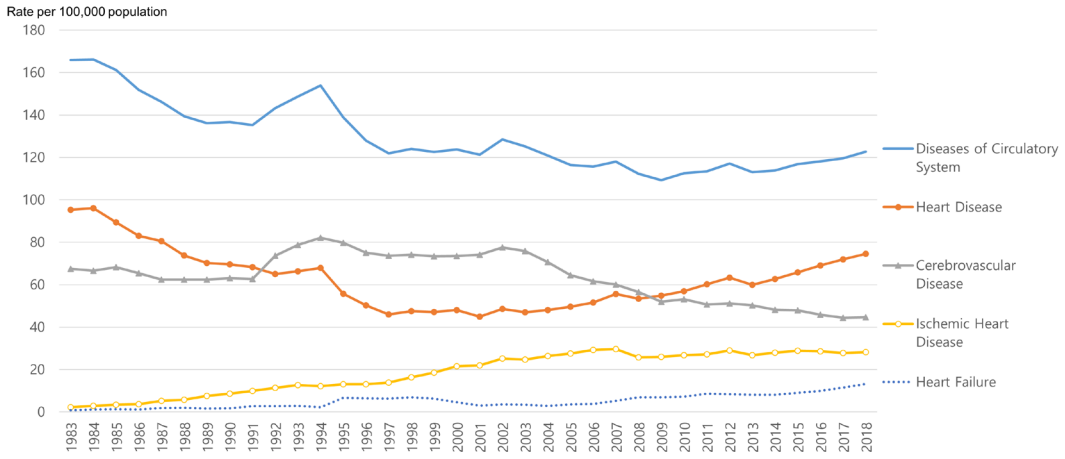


Figure 2. Crude mortality from cardiovascular disease in Korea, 1983-2018. (Data Source: Causes of Death Statistics, Statistics Korea)

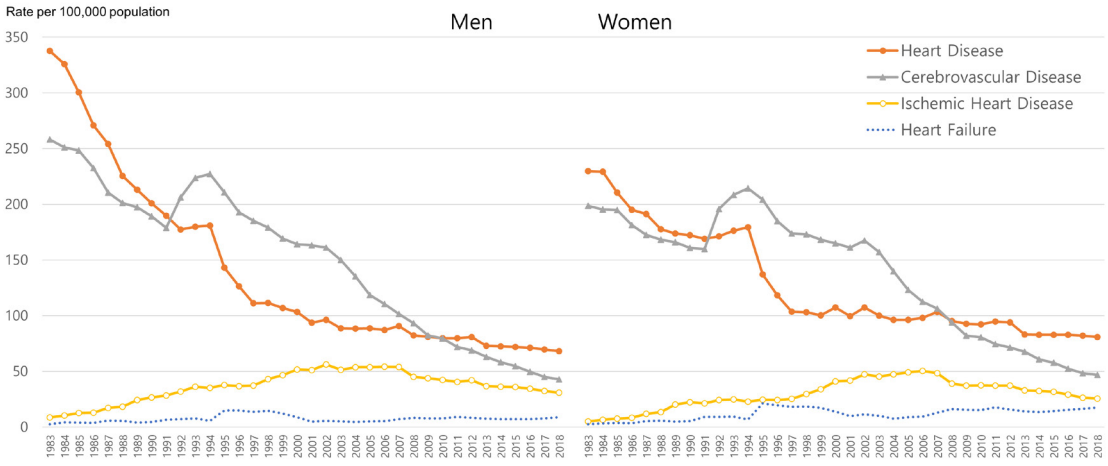


Figure 3. Age-standardized mortality from selected cardiovascular diseases in Korea, 1983-2018. (Data Source: Causes of Death Statistics, Statistics Korea)

the absolute level and time trends of the incidence and prevalence of CVD in Korea. Reviewing the published results of recent Korean studies (*9-16*), it is presumed that the prevalence of overall CVD is increasing, and the incidence rate will vary depending on the subtype of CVD. Recently, a growing number of studies try to estimate the disease burden of major CVDs using the National Health Insurance (NHI) claims data which covers all Korean residents (*9-11,13,15-21*). The estimated incidence and prevalence rates may vary from study to study, because of the differences in the working definition of CVD diagnosis or in the methods of identifying new-onset events (*22,23*). However, if we interpret them carefully, these data would be useful for understanding the magnitude and trends of CVD, because the NHI data include medical service uses of the entire Korean population (*24,25*).

Recent studies using NHI data report the incidence of acute myocardial infarction in the range of 50-70 cases per 100,000 person-years in men and 20-30 cases per 100,000 person-years in women (*13,16,17,19,21*). The crude incidence rate of acute myocardial infarction has been decreasing since peaking in 2006-2007, but it has recently returned to rise (*13,16,17*). However, the age-adjusted incidence of myocardial infarction is not increasing, and the crude incidence appears to

be increasing due to the increasing number of elderly people. Although it is not as big as in other countries, regional and socioeconomic differences in the incidence of acute myocardial infarction are also observed in Korea (*13,18*). The age-standardized incidence of acute myocardial infarction has been reported to be higher in the southeastern region compared to other parts of Korea (*13*). A study based on the NHI claim data of the year 2005 estimated prevalence of coronary heart disease and acute myocardial infarction at 2.38% and 0.31% for men and 2.53% and 0.20% for women, respectively (*18*). Another study based on the NHI claim data, reported that the prevalence of acute myocardial infarction increased from 0.38% to 0.46% between the year 2007 and 2012 (*11*).

The incidence of cerebrovascular disease showed different trends by types of hemorrhagic stroke and ischemic stroke. Hemorrhagic stroke was a major type of cerebrovascular disease before the 2000s, but the rate of hemorrhagic stroke has decreased rapidly and currently ischemic stroke accounts for about two-thirds of all strokes in Korea. Recent data suggest that age-standardized incidences of overall stroke, ischemic stroke, and hemorrhagic stroke are all decreasing in Korea (*10,14,16,19*). The prevalence of stroke in the adult population in Korea was reported to be 1-2%, and the prevalence rate is estimated to be increasing despite the decrease in the incidence of stroke (*10,14,19*).

Unlike other kinds of CVD, heart failure shows rapidly increasing trends all in mortality, incidence, and prevalence. These increasing trends are observed even after age standardization (*9,20*). Another characteristic that heart failure is different from other CVDs is that it occurs more in women than in men. Between the year 2002 and 2013, the prevalence of heart failure increased from 0.54% to 1.34% in men, and from 0.96% to 1.72% in women (*20*).

A very recent Korean study reported a much higher incidence and prevalence of CVDs, compared to other studies. In this study, the prevalence of total atherosclerotic CVD, ischemic stroke, and acute myocardial infarction were 10.11%, 1.86% and 0.56% in 2015, and the corresponding incidence rates were 6,994, 630 and 236 per 100,000 person-years, respectively (*15*). However, this study seems to have overestimated the rates because it used wider range of diagnosis codes compared with other studies, and it included any cases with CVD diagnosis codes regardless of primary or secondary diagnosis, and inpatient or outpatient clinics. Figure 4 shows the trends of hospitalization rate for cerebrovascular disease, ischemic heart disease, acute myocardial infarction, and heart failure from 2002 to 2018, which were based on codes for primary admission diagnosis in the NHI claim database.

Major risk factors of CVD

The change in incidence and dominant subtypes of CVD can be projected by the changes in cardiovascular risk factors (*26*), because a large portion of CVD risk is explained by the major modifiable risk factors such as high blood pressure, abnormal blood lipids, diabetes, overweight/obesity, and cigarette smoking (*27,28*). It is known that established risk factors such as high blood pressure, hyperlipidemia, diabetes, and smoking are major risk factors for CVD also in Korea (*29*) and other Asian populations (*30*). However, since the distribution of individual risk factors is changing, observing them will help predict changes in CVD incidence and subtype distribution in the near future (*31*). Among the major

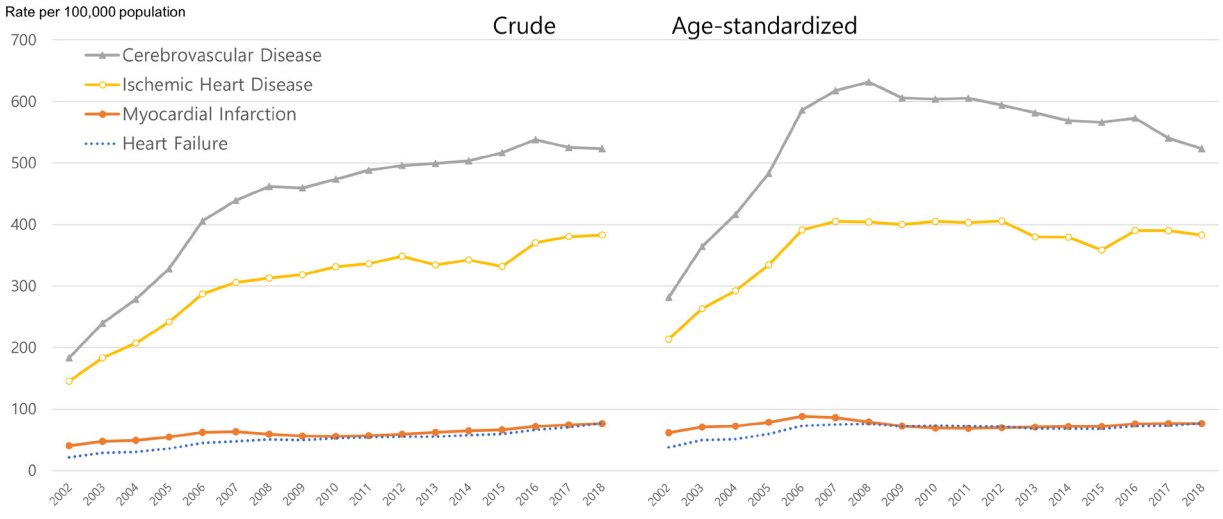


Figure 4. Crude and age-standardized hospitalizations for selected cardiovascular diseases in Korea, 2002-2018. (Data Source: National Health Insurance Database)

modifiable risk factors, cigarette smoking is a strong risk factor for most CVD subtypes, high blood pressure is more strongly related to cerebrovascular disease, especially hemorrhagic stroke, and hypercholesterolemia and diabetes are more closely related to ischemic heart disease (*32-35*).

We can observe the distribution of cardiovascular risk factors and their changes among Koreans, by reviewing the publications analyzing national representative datasets, such as the Korea National Health and Nutrition Examination Survey (KNHANES), the National Health Screening Program, and the NHI claims (*36,37*).

The prevalence of obesity defined as a body mass index ≥ 25.0 kg/m^2, according to the Asia-Pacific Region definition and the Korean Society for the Study of Obesity (KSSO) guideline (*38,39*), was 35.7% among Korean adults aged 30 years or older in 2018. The prevalence of obesity is increasing in all ages, but in sex-specific analysis, the prevalence is increasing faster in men but the increasing trend is less significant in women. During the decade 2009-2018, the prevalence of obesity increased from 29.7% to 35.7% in the whole adult population, from 35.6% to 45.4% in male adults, and from 23.9% to 26.5% in female adults. Abdominal obesity shows a similar pattern. The prevalence of abdominal obesity, defined as a waist circumference of at least 90 cm in men and 85cm in women according to the KSSO criteria (*38*) was 23.8% in the total population, 28.1% in men, and 18.2% in women, recorded in 2018 (*40,41*).

The average level of blood pressure and the prevalence of hypertension of Korean adults have shown little change in the recent 10 years. Currently about 30% of Korean adults aged 30 or older have hypertension (*12,31,42*). However, according to the increase in the elderly population, the number of people with hypertension increased steadily, exceeding 11 million (*42*). Based on the NHI claims, the number of people diagnosed with hypertension increased from 3 million in 2002 to 8.9 million in 2016. The number of people using antihypertensive medication increased from 2.5 million in 2002 to 8.2 million in 2016. However, only 5.7 million people are persistently using antihypertensive medication (*24,42*). Based on the KNHANES data, hypertension awareness, treatment, and control rates increased fast until 2007, but showed a plateau thereafter (*36,42*). To achieve further improvement in hypertension management, it is important to increase awareness and treatment rates for younger people with hypertension, because awareness and treatment rates are below 50% among the young hypertensive patients aged less than 50 (*43,44*). It is another challenge to manage hypertension of elderly people who are increasing in absolute number and suffering from multiple chronic disorders (*45*).

The prevalence of diabetes among adults aged 30 years or older was 14.4%, when diabetes was defined as satisfying at least one aspect of physician diagnosis: current use of anti-diabetic medications, high fasting plasma glucose (FPG ≥ 126 mg/dL), or high hemoglobin A1c (HbA1c ≥ 6.5%) (*46,47*). Another 25.3% have an impaired fasting glucose level, defined as FPG of 100 to 125 mg/dL. The prevalence of diabetes was higher in men (15.8%) than in women (13.0%) and relatively higher among elderly people (29.8% in age 65 or older). However, the prevalence of diabetes became higher in women than in men (33.6% *vs.* 29.1%) after age 70. The prevalence of diabetes is increasing from 12.4% in 2011 to 14.4% in 2016, with a similar trend for men and women. The awareness and treatment rates of diabetes were 62.6% and 56.7%, respectively, but the control rate, defined by a HbA1c < 6.5%, was only 25.1% in 2016 (*12,40,47*).

In Korea, hyperlipidemia or dyslipidemia is on the rise overall, but it varies depending on its subtype and population characteristics (*31,48,49*). Based on the KNHANES, the prevalence of hypercholesterolemia, defined as a total cholesterol level ≥ 240 mg/dL (*50*), among adults aged 30 or older has increased from 14.4% in 2012 to 19.9% in 2016 (*40*). When the dyslipidemia was defined as satisfying at least one of the following: elevated low-density lipoprotein cholesterol (LDL-C ≥ 160 mg/dL), decreased high-density lipoprotein cholesterol (HDL-C < 40 mg/dL), hypertriglyceridemia (TG ≥ 200 mg/dL), or current use of lipid-lowering medication, the prevalence of dyslipidemia was very high at 40.5% of the total, 47.9% in men and 34.3% in women. The elevated LDL-C was relatively high in women in their age 60s (39.9%) compared to men or women of other ages. Prevalence of hypertriglyceridemia was 17.5% of the total, being much higher for males than females (24.8% *vs.* 11.0%) (*40*). Triglyceride levels increased with age in women, but in men, it increased rapidly during younger adulthood, peaking at 50-54 years, and then decreased. Therefore, female seniors have higher triglyceride levels than men of the same age (*48*). Although the number of Korean adults taking lipid-lowering drugs is increasing rapidly, many of them do not use medication persistently, so it is necessary to increase compliance with drug treatment (*40*).

Cigarette smoking has long been the greatest cause of CVD and other non-communicable diseases. A Korean study reported that smoking contributed to 41% of coronary heart disease and 26% of strokes in Korean men (*51*). Korean data indicate that cigarette smoking is a major modifiable risk factor for type 2 diabetes: smoking is associated with diabetes incidence and mortality (*52*), and smoking cessation has been shown to reduce the risk of developing diabetes among smokers (*53*). The smoking rate for adult Korean males was very high at 79% in 1980, but fell to below 50% for the first time in 2007 (45.1%), and to less than 40% in 2015 (39.4%), and further decreased to 36.7% in 2018.

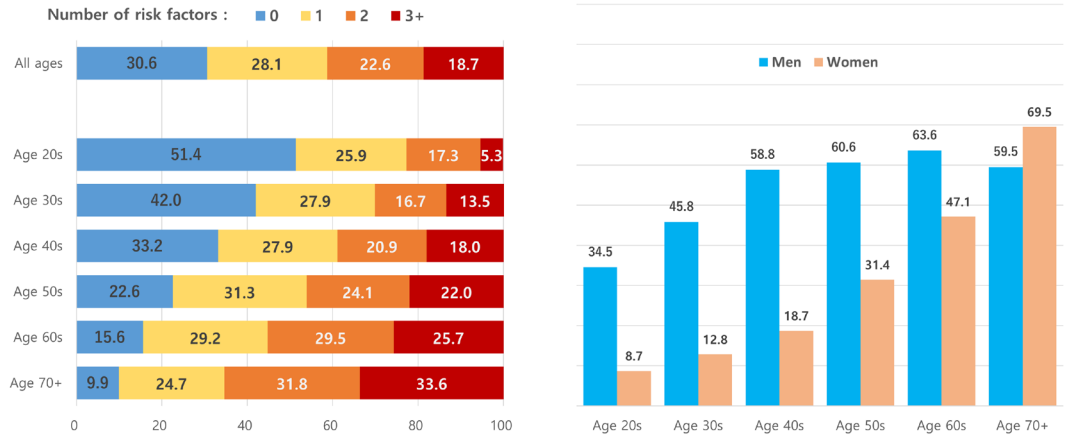


Figure 5. Distribution of number of cardiovascular risk factors by age and sex in Korean adults. Risk factors include hypertension, diabetes, hypercholesterolemia, obesity, and cigarette smoking. (Data Source: The Korea National Health and Nutrition Examination Survey, 2018)

Smoking rates in adult females were much lower than that in males, but it is increasing slowly but persistently (5.2% in 2001; 6.3% in 2010; 7.5% in 2018) (*12*). Reports have also indicated that smoking rates differ by age and socio-economic status. Lower household income was also associated with a higher smoking rate in both men and women, but this association was stronger in women. The smoking rate was 4% in women of the highest income quartile, but 11% in those of the lowest income quartile (*31*).

Since a person often has more than one risk factor, it is also necessary to evaluate multiple cardiovascular risk factors as well as individual risk factors. Figure 5 shows the combined prevalence of five major cardiovascular risk factors including hypertension, diabetes, hypercholesterolemia, obesity, and smoking among Korean adults. Seventy percent of Korean adults (≥ 20 years old) have at least one risk factor, 41% have ≥ 2 risk factors, and 19% have ≥ 3 risk factors. Exposure to multiple risk factors increases with age, with 65% having ≥ 2 risk factors and 34% having ≥ 3 risk factors in those aged 70 years or older. Men and women show a different pattern in the prevalence of cardiovascular risk factors. In men, exposure to multiple risk factors rapidly increases during the middle ages, but shows little change after their 60s. On the other hand, in women, exposure to multiple risk factors increase continuously during their life time. Thus women aged 70 years or older have more risk factors than men of the same age. As the elderly female population is rapidly increasing in Korea, it is a challenge to develop CVD prevention strategies targeted for elderly women with multiple risk factors.

In summary, Korea has had the fastest decline in CVD mortality in the world, but the burden of CVD is still increasing due to the rapid aging of the population and the increasing number of patients with prevalent CVD, and this trend is expected to continue. Cerebrovascular disease is decreasing in both incidence and mortality rates. Ischemic heart disease is decreasing in mortality rates, but the decrease in incidence is not clear yet. Heart failure is quickly increasing both in incidence and mortality rates. Among cardiovascular risk factors, control of high blood pressure has improved a lot, but there is room for further improvement. Smoking rate is decreasing significantly but is still high in men, and it is increasing in women. Obesity, diabetes, and hypercholesterolemia are increasing, and measures are needed to reverse these trends. As the elderly population, especially those with multiple risk factors and chronic disorders, is increasing, the management of this high-risk group will be an important challenge to prevent CVD in Korea.

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The use of Japanese long-term care insurance claims in health services research: current status and perspectives

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Abstract: This study aims to evaluate the current status and perspectives on the use of Japanese long-term care (LTC) claims databases for research. We conducted a comprehensive literature search of PubMed and the Japan Medical Abstracts Society (Ichushi-Web), focusing on LTC claims data analyses published between 2000 and 2020. We summarized the study characteristics, database characteristics, and the research areas related to health services that were studied. In total, 86 journal articles (12 in Japanese and 74 in English) were included in our review. A particularly remarkable increase in the number of publications from 2016 to 2020 was observed. We extracted more publications with combined databases (n = 64) than those that only used a single source of the LTC claims databases (n = 22). More than half of the studies analyzed healthcare expenditure, healthcare utilization, and quality of care which were relevant to health services research. The most frequently mentioned limitation was the lack of validation in variables stored in the LTC claims databases. In conclusion, the LTC claims databases could serve as important sources of information for the evaluation of healthcare delivery, quality of care, and LTC policy.

***Keywords*:** long-term care claims, administrative data, health services research

Introduction

In 2000, along with the implementation of the long-term care (LTC) insurance system, the Japanese government implemented a standardized electronic LTC claims system with the primary aim of saving money by reducing paper costs and improving the efficiency of access to information on LTC users. Recently, LTC claims have become highly valued by LTC providers, researchers, and policymakers because they offer timely and important information to enhance their decision making.

LTC claims, simply put, are bill records that LTC service providers submit to insurers. They comprise detailed information on the types of LTC services, amount of care granted, and associated payments. Municipal governments, as LTC insurers, have established National Health Insurance Organizations and collected LTC claims aiming to pay the insured cost for their residents after examining the claims. Along with LTC claims, municipal governments also store the care-needs certification survey data (*1*).

To receive LTC insurance services, older people should contact the municipal government and obtain a care-needs level certification after a care-needs assessment. The care-needs certification survey contains 73 items regarding current physical and mental status. The assessment result and primary care physician's statement will be submitted and discussed by the Nursing Care Needs Certification Board that determines and assigns the care-needs level (*2*). Because the primary care physicians' statements are still paper-based, there is much difficulty in providing the necessary data for analysis.

Since LTC claims databases (which we defined as both LTC claims and care-needs certification surveys) reflect real-life LTC provisions and functional changes of care recipients, the data were initially used by the government to grasp the current situation of LTC services and review the LTC system. Ever since, LTC claims have attracted the attention of researchers – especially in health services research (HSR) – because of their extensive information that is useful for evaluating healthcare service delivery, quality, and policy development. Researchers initially accessed these data after the conclusion of joint research (between their university and the municipal government) related to LTC claims database analysis. Subsequently, the Ministry of Health, Labour and Welfare (MHLW) began providing national LTC claims under Article 33 of the Statistics Act (*3,4*). Only researchers who were funded by or undertook joint research with the government were allowed to use this data. Soon after, the MHLW of Japan developed expansive national-

level databases named "National LTC Claims Databases (Kaigo DB)" by collecting anonymous LTC claims and care-needs certification surveys, which it publicly released in 2018. The "Kaigo DB" was only available to national or local government agencies, universities, and other quasi-public corporations (*1*). To use these data, study protocols had to be approved by the advisory committee of the MHLW (*1*). Owing to universal health coverage for LTC (*5*) and a well-established payment computing system, Japan became one of the few countries that maintain national-level LTC claims. Despite governments and researchers having great expectations of utilizing the data, little is known about the current status of LTC claims, such as the number of publications, research type, topic, as well as their limitations.

As mentioned above, LTC claims databases record accurate information about the structure (*e.g.*, human resources and organization characteristics), process (*e.g.*, provision of LTC services), and outcome of care services (*e.g.*, changes in the care-needs level, incidence of dementia, and discharge to home), and thus, is of great value in evaluating concerns relevant to HSR.

Therefore, this study aims to not only provide an overview of the current status and perspectives on Japanese LTC claims database analysis by conducting a comprehensive literature review, but also to synthesize current evidence of LTC claims database analysis in HSR.

Comprehensive search of LTC claims-based studies

Search strategy and selection criteria

We conducted a comprehensive literature search of the electronic databases of PubMed and the Japan Medical Abstracts Society (Ichushi-Web), following the methods recommended by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (*6*). All searches within titles, keywords, and abstracts covered the period from January 1, 2000 to November 30, 2020. The following search terms were identified: ("long-term care" OR "long-term care insurance") AND ("claim" OR "administrative data" OR "claims" OR "data" OR "database" OR "databases" OR "certification survey") AND ("Japanese" OR "Japan"). We limited the publication language to English and Japanese.

First, duplicated studies were removed from the extracted list. A study was included if it used LTC claims data as the principal source to address its research objectives. Thus, we excluded letters, editorials, conference abstracts, posters, oral presentations, and project reports. We also conducted a manual search to include studies not identified by the automated search.

Data extraction

The authors screened the citations based on the inclusion and exclusion criteria. Data relevant to the study characteristics (publication year, study design, and setting), and data source combinations were decided after a consensus was reached among the authors. For every journal article, we defined the research area according to the subject categories of the SCImago Journal & Country Rank (*7*). For HSR studies, we summarized the detailed information on outcomes, exposures, and main findings.

Description of identified LTC claims-based studies in Japan

Figure 1 depicts the study selection process. The initial combined search retrieved 438 journal articles. After removing the duplicates, 435 articles were assessed for eligibility, of which 78 full texts were included in this review. Eight articles were identified through manual searches.

Publication characteristics

The first study using LTC claims was published in 2006, and the number of publications increased significantly from 2016 (Figure 2). Among the total publications, 86% were written in English and the most common journal was *Geriatrics & Gerontology International* (10.5%), followed by *BMC Geriatrics* (7.0%). The five most commonly researched areas were geriatrics and gerontology (36.0%), medicine (miscellaneous) (33.7%), health policy (17.4%), public health, environmental, and occupational health (10.5%), and psychiatry and mental health (9.3%) (Table 1).

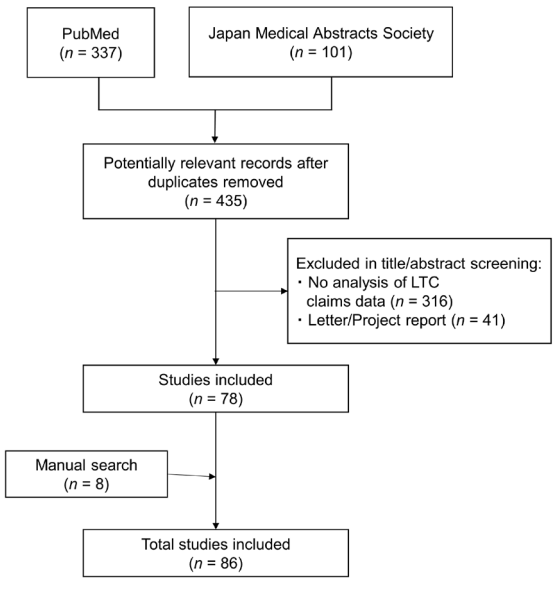

Figure 1. Study selection process.

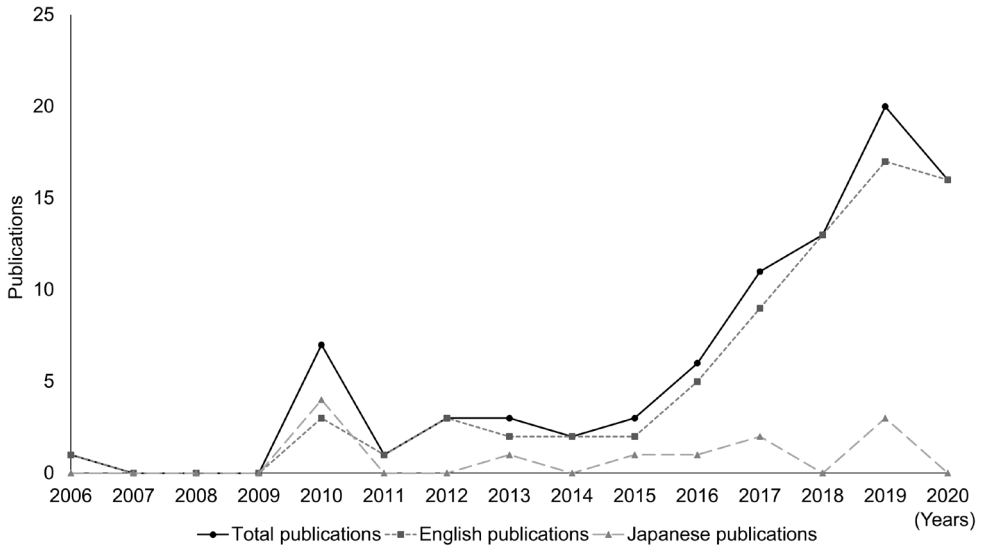

Figure 2. Frequency of publications using LTC claims data.

Table 1. Publication characteristics (*n* = 86)

	n	%
Language		
English	74	86.0
Japanese	12	14.0
Journal		
Geriatr Gerontol Int	9	10.5
BMC Geriatr	6	7.0
BMC Health Serv Res	4	4.7
Journal of Health and Welfare Statistics	4	4.7
PLoS One	4	4.7
J Am Med Dir Assoc	3	3.5
J Gerontol A Biol Sci Med Sci	3	3.5
Others	53	61.6
Research area[a]		
Geriatrics and gerontology	31	36.0
Medicine (miscellaneous)	29	33.7
Health policy	15	17.4
Public health, environmental and occupational health	9	10.5
Psychiatry and mental health	8	9.3
Epidemiology	7	8.1
Multidisciplinary	4	4.7
Others	13	15.1

[a]Multiple choices possible.

Table 2. Database characteristics

	n	%
LTC database components used		
LTC claim	44	51.2
Care-needs certification survey	38	44.2
Both	4	4.7
National level		
Yes	14	16.3
No	72	83.7
Data source combination[a]		
Medical claim	19	22.1
The Ohsaki Cohort	19	22.1
Death records	4	4.7
Survey of institutions and establishments for long-term care	2	2.3
Tsurugaya Project	2	2.3
Other surveys	19	22.1
No database combination	22	25.6

[a]Multiple choices possible

Database characteristics

Table 2 provides an overview of database characteristics. The most frequently used data were LTC claims (55.8%), and 48.8% of the total studies used the care-needs certification survey. Judging from the data size, studies that used national-level LTC claims accounted for 16.3% of the total. There was significant use of linkage data (74.4 %) compared to a single source of LTC claims data (25.6%). The most frequent data combinations were medical claims (22.1%) and the Ohsaki Cohort Study (22.1%). Four studies that linked with death records reported a probabilistic matching process for data combination.

Study characteristics

The most common study design was the cohort study (62.8%), followed by cross-sectional studies (27.9%). Study participants included LTC service users (both home and community, and LTC facility) in 35 studies (40.7%), while 20 studies (23.3%) targeted at-home and community users. Independent people who were not qualified for the LTC insurance system at baseline were included in 27 studies (31.4%). Among all the studies, the most common outcome was the onset of functional disability (20.9%), which is defined as the point at which a participant was certified in the LTC insurance system (Table 3).

The use of LTC claims in HSR

More than half of our examined studies were HSR

Table 3. Study characteristics of empirical (*n* = 85) and methodological (*n* = 1) publications

	n	%
Study design		
Descriptive	4	4.7
Cohort	54	62.8
Case-control	3	3.5
Cross-sectional	24	27.9
Methodological	1	1.2
Study outcomes		
Incidence of functional disability	18	20.9
Health expenditure	13	15.1
Incidence of dementia	13	15.1
Care-needs level change	10	11.6
Long-term care service utilization	7	8.1
Others	25	29.1
Study setting		
Home and community	20	23.3
LTC facility	4	4.7
LTC facility and home and community	35	40.7
Independent people	27	31.4

studies (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=21*). These studies analyzed the healthcare structures (*e.g.* service providers' characteristics, staffing levels), the utilization of LTC services and their impact on health outcomes. Among these HSR studies, the most frequent outcomes were healthcare expenditure (*i.e.*, LTC or medical expenditure or both), LTC service use, and change in the care-needs level.

Discussion of current status and perspectives of LTC claims analysis

This comprehensive review showed that LTC claims were increasingly used in scientific analysis, and this increase was particularly remarkable between 2016 and 2020. Most of the studies were empirical and written in English. Moreover, they focused on a variety of research areas, showing the widespread use of LTC claims. Additionally, more than half of all studies were HSR studies, which examined how LTC beneficiaries gain access to LTC care, how much care costs, and what happens to the beneficiaries after they receive care.

Although there was a notable increase in the number of publications regarding LTC claims database analysis, the total number was far smaller than that of medical claims analysis. One possible reason is that medical researchers commonly prioritize prevention and cure over LTC. However, Japan has the highest aging rate in the world, with one-quarter of its population aged 65 or over. As known to all, older people are more likely to suffer from multiple chronic conditions (*8*). Therefore, medical research studies that can benefit an aging society are in urgent need. This issue was emphasized by the Science Council of Japan in 2014, which claimed that the goal of medicine should switch toward maximizing the quality of life (QOL) for the patient through "community-oriented medical care" that requires close collaborations among public health officials related to medical activities and LTC (*9*). Analyzing linkage data between medical and LTC claims could provide evidence regarding the cooperation between medical and LTC professionals.

Another reason for the large number of publications using medical claims is the involvement of the private sector. The JMDC company has collected medical claims from multiple health insurance associations since 2005, providing the data to healthcare companies, universities, as well as governments. As of 2020, the JMDC claims database includes approximately 7.3 million subjects. The total number of publications has reached 289 since their provision of data (*10*). If such a provision system became available for LTC claims, rapid progress can be made in the LTC research area. Undoubtedly, data provision should be guaranteed by sufficient security and privacy protections.

Most studies using single LTC claims highlighted the lack of information on detailed medical conditions (*11-15*). The reason was the difficulty in investigating the effect of LTC service uses without adjusting for the medical conditions of older people. Linkage data between LTC and medical claims solved this problem and were commonly used in most studies. However, the combination of LTC and medical claims were only available in some municipalities, resulting in the problem of generalizability. Recently, the Japanese government publicly released a nationwide linked database between medical and LTC claims in October 2020; future studies using this data are thus warranted. The other frequently combined data was the Ohsaki Cohort Study data, which is a large population-based prospective study that focuses on psychosocial factors and LTC certification status (*16*). Almost all studies using this combined data treated the incidence of functional disability or dementia as outcomes and examined the association with psychosocial factors such as education level, citrus consumption, and psychological distress (*17-20*). LTC certification survey data were only used to detect the outcomes of studies. For example, the date of obtaining LTC certification was considered as the incident date of functional disability. Because LTC services are only provided after a person becomes certified for LTC, the topics of these studies offer no insights into LTC services.

The most frequent research design was the retrospective cohort study. The care-need levels were most commonly tracked in cohort studies because LTC claims recorded this information in an accurate and timely manner. There were only four descriptive studies, although they were the most common study design in other claims data analysis such as the Japanese national database of health insurance (NDB) (*21*) and Canadian health insurance claims (*22*). In Japan, Matsuda and colleagues published a series of

more than 30 Japanese papers focusing on the analysis of linked databases between LTC and medical claims from 2018 to 2020 (*23*). These studies were helpful in grasping the current status of LTC services because they provided rich information in terms of LTC service access, utilization, health outcomes, and quality of care. We excluded them because these papers are comments-oriented which did not satisfy our selection criteria of the original research article.

Like other health administrative databases, the primary advantage of LTC claims databases is the typically large sample that provides high generalizability and statistical stability. Another distinctive advantage over medical claims is the possibility of evaluating the QOL of LTC beneficiaries. The care-needs level of LTC claims is highly correlated with the Barthel Index (*24*), which may because the questionnaire assessing the care-needs level contains many items related to activities of daily living (ADL) and instrumental activities of daily living (IADL). Lawton indicated that the functional health of ADL and IADL is an important aspect of the QOL in frail elders (*25*).

The use of LTC claims databases in HSR has advantages to answering the following questions correctly: What benefits were provided to whom, when, and in what amount? Therefore, it has been widely used in evaluating the quality of care. For instance, studies have examined the effect of demographic factors, financing systems, and organizational structures and processes on health outcomes in terms of functional decline, discharge to home, physician visit frequency, length of hospital stay, and residential care admission. Topics regarding healthcare expenditure and health service utilization were also frequently investigated in HSR studies.

A common limitation of HSR studies using LTC claims was the lack of validation of outcome measures. As Swart *et al.* pointed out, in claims data analysis, a comprehensive validation process that adheres to the official guidelines is recommended to ensure data accuracy (*26,27*). Matsuda *et al.* clarified the validity of Japanese LTC care needs levels by testing their correlation with the Barthel Index (*24*). To better understand the LTC claims information, it is essential that studies be validated.

The present study is not without limitations. The selection of keywords for the research strategy was challenging because there was variation in the translation of LTC claims in English. We restricted our analysis to the most common keywords of "claims data," "databases," and "administrative data." Despite this wide search strategy, we might have failed to extract some relevant publications.

Conclusion

In conclusion, our study analyzed the use of Japanese LTC claims databases in research publications to provide an overview of the current status and perspectives. From 2016 to 2020, we found a particularly remarkable increase in the number of publications, more than half of which were HSR studies providing comprehensive information regarding the quality of care, healthcare expenditure, and LTC service use. Moreover, these HSR studies highlighted useful documents for evidence-based policy regarding LTC.

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Proton therapy for patients with esophageal cancer: History, characteristics, clinical outcome and future direction of proton beam therapy

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Abstract: After the second war, Wilson who participated in development of the atomic bomb in Los Alamos studied peaceful use of atomic energy and proposed a property of proton beam that has potential to treat cancer. According to his proposal, the first patient was treated with proton beam therapy at the University of California Berkley in 1954. The first series of proton beam therapy for patients with esophageal cancer was reported from Japan in 1993. After that many proton facilities in Japan reported the clinical outcome of patients with esophageal cancer. Many dosimetric and clinical studies showed proton beam therapy for esophageal cancer was less toxic than photon beam therapy, however there is a paucity of randomized trials and evidence that proton beam therapy has clearly superior survival compared to photon therapy. Only one randomized trial has been conducted to study less toxicity for proton beam compared with intensity modulated radiotherapy (IMRT), which was stopped early because toxicities of IMRT were higher. A phase III study comparing overall survival between proton beam therapy and IMRT is now activated. A cost reduction for proton therapy is necessary to facilitate patient care and establishment of clinical evidence.

***Keywords*:** proton beam therapy, esophageal cancer, particle beam therapy

Introduction

Proton beam therapy provides superior distribution of a high dose to tumors and low dose to normal tissue compared with photo beam (*1*). In the beginning of proton therapy for esophageal cancer, Japanese researchers played the main role for clinical application of proton beam therapy. Among various types of charged particles, now proton beam is the most widely used for esophageal cancer in the world.

In this article, we review dosimetric analysis of a proton plan for clinical results of reduced toxicity and survival, and discuss future directions of proton beam therapy.

History of proton beam therapy

Proton beams have a very rapid energy fall in the deep penetration site, which is known as the Bragg peak. This phenomenon was first reported by Sir William Henry Bragg in 1904 (*2*). Robert Wilson noted in 1948, using the Bragg peak, that a proton beam achieves desirable dose coverage of tumor volume and a therapeutic advantage for cancer compared with a photon beam (*3*). A dose distribution of protons is steep near the tumor and rapidly falls off behind the tumor (Figure 1). In 1954, the first proton therapy on humans was done for pituitary metastasis disseminated from breast cancer at the University of California Berkeley (*4*). After that proton therapy began at Uppsala, Sweden, Cambridge, United States of America and so on. In 1974, Suit *et al*. initiated studies of fractionated proton beam therapy for chordoma and chondrosarcoma at Harvard University (*1*). First proton therapy for uveal melanoma was also done at Harvard University (*5*). From their achievement, standard therapy for chordoma near the skull base and uveal melanoma even now use proton beam therapy. The largest number of patients with these cancers, in the world, are treated by proton beam. Contrary to this proton beam therapy is little used for thoracic, abdominal and pelvic cancer in 1900's.

In 1993 from Japan, Tsujii *et al*. reported results of proton beam therapy for these tumors included esophageal cancer at the University of Tsukuba (*6*). Nineteen patients with esophageal cancer were treated by proton beam. Seven patients underwent proton beam only with median dose of 78.5 Gy given in a median of 26 fractions. The other 12 patients were treated with photon proton with proton beam. The median combined total dose was 80.2 Gy. The overall survival rates at 3-years were 100% for Stage I, 60% for Stage II, and 50% for Stage III, respectively. They reported that the

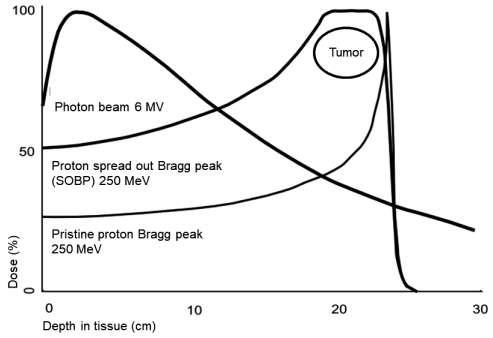

Figure 1. The shape of depth-dose curves for photon beam (6 MV), pristine proton Bragg peak (250 MeV) and scattered spread out Bragg peak (SOBP) proton beam. SOBP covers tumor well and energy is rapidly decreased behind the tumor. The energy of scattered SOBP proton beam is higher than pristine proton beam.

toxicity appeared to be minimum, even though the irradiated dose was higher than a conventional dose. To the best of our knowledge, this report is the first series of esophageal cancer that underwent proton beam therapy.

Characteristics of proton beam therapy

The proton beam is made from helium ions and accelerated using a cyclotron or synchrotrons to 230 MeV and more energy. The pristine proton beam generated from the accelerator is a narrow beam. For clinical use, in the two methods a "scattering" and "scanning" technique develop. The passive "scattering" method is spread out of the Bragg peak (SOBP) through the compensator (Figure 1). In this traditional proton beam therapy, the doses proximal to the tumor is similar to those of a photon. The new technique called active "scanning" develops, which is capable of being intensity modulated proton therapy (IMPT). IMPT is enabled to reduce the dose near the proximal site of the tumor. Hence, IMPT achieves an ideal dose distribution of protons, which consists of a low dose at the entrance, flat at the tumor and rapid fall off behind of the tumor.

The biological effect of radiation is different in organs and source of radiation. Comparing physical absorbed dose from different radiation sources, a coefficient named the relative biological effectiveness (RBE) is employed to compare the ratio of biological effectiveness of one type of ionizing radiation to another. Protons have a comparable similar biological effect as photon therapy. Many proton centers use RBE of protons as approximately 1.1. Contrarily Uppsala in Sweden use RBE as 1.0 as University of Tsukuba in Japan formerly used. The equation below is used to convert absorbed photon dose into proton absorbed dose.

Photon (Gy) = RBE (1.0 or 1.1) × Proton (Gy)

The dose distributions of a proton beam are very sensitive to variation in tissue density through the beam pathway. The precise tissue density is necessary to evaluate by CT scanning and planned by advent of a treatment planning computer system. The control of organ motion or confirmation of tumor location by image guide are important to irradiate an accurate dose. The methods of breathing control, 4-dimentional (4D) planning CT, insertion of fiducial marker and image guide were developed for proton beam therapy and subsequently introduced to photon therapy.

Dosimetric advantage of proton therapy

Intensity modulated radiotherapy (IMRT) is widespread, which method delivers a photon beam more conformed to tumor and less to normal tissue, however an IMRT irradiated low dose of photons go around the tumor. Many showed a dosimetric advantage of even passive scattering from a much more active scanning proton beam compared with those of IMRT (*7*-*13*), because the dose of proton beam was a little behind the tumor. We review the dosimetry advantage, clinical outcome and future directions.

Esophagus is located at center of thorax and along the lung and heart. Lung is sensitive to radiation and has a risk of radiation pneumonitis. Heart is also at risk for pericarditis, cardiac effusion and myocardial infarction. To reduce such toxicities, lower dose of organ risk is ideal in a dosimetric plan. In modern radiotherapy, a CT scanning based dosimetric plan is calculated by a treatment planning computer.

Isacsson *et al*. described a passive proton beam plan reduced dose of the heart, lungs, spinal cord and kidneys compared with a photon beam plan in five patients with esophageal cancer (*8*). Zhang *et al*. showed a superior lung spring effect of passive proton plan to photon plan in 15 patients with distal esophageal cancer. They showed the maximum dose of spinal cord in 3-dimentional (3D) CT plan exceeded 5 Gy in that of 4-dimentional (4D) CT plan in proton beam therapy because of variations in stomach gas filling (*13*). This study warned precise planning is needed for a proton beam plan. Ling *et al*. also described the advantage of a passive proton plan compared to that of 3D conformal radiotherapy (CRT) and an IMRT plan in ten patients with esophageal cancer. They showed a proton plan consistently decreased the dose on the heart and lung compared with both 3D CRT and IMRT (*9*). Hirano *et al*. reported 27 patients with clinical stage III esophageal cancer compared among passive proton plan, 3D-CRT plan and IMRT plan in a dosimetric analysis. They showed proton plan reduced the dose of risk organs, especially lung and heart (*7*).

Shiraishi *et al*. demonstrated the heart dose of 727 patients with esophageal cancer comparing between proton and IMRT plans. The number of passive scanning proton therapy and IMPT were 237 and 13, respectively. They showed the proton beam plan resulted in significantly lower radiation exposure to the heart than IMRT plan. IMPT showed a significant decreased dose

to heart compared with passive scanning proton (*10*). Zeng *et al*. demonstrated a comparison of beam direction of scattering proton and IMPT for 11 patients with esophageal cancer. Three beam directions, posterior-anterior (PA), anterior-posterior/posterior-anterior (AP/PA) and posterior-anterior/left posterior oblique (PA/LPO) were compared. IMPT reduced the dose of proximal site of tumor compared with scattering proton beam. They showed proton therapy with a single PA IMPT was the most reduced dose for lung (*12*). These two studies showed the advantage of IMPT compared with scattering proton beam.

Warren *et al*. showed scanning proton plan reduced thoracic vertebrae dose compared with a bone marrow sparing volumetric modulated arc therapy (VMAT) plan in 21 patents with mid-esophageal cancer (*11*). They speculated a reduced dose of vertebral bone marrow by proton beam has potential to reduce acute toxicities in concurrent chemoradiotherapy for esophageal cancer.

Reduced clinical toxicities of proton therapy

There were several clinical reports, which described proton beam therapy reduced toxicities compared with photon therapy. Makishima *et al*. from University of Tsukuba showed an advantage of dose histogram for passive proton beam therapy and retrospectively compared adverse events (n = 24) with photon (n = 13) beam. Radiation pneumonitis and cardiac effusion was significantly reduced using proton beam therapy (*14*). Wang *et al*. from MD Anderson Cancer Center reported they compared gastrointestinal and pulmonary complication among 444 patients treated with 3D-CRT, IMRT and passive proton beam therapy. The proton beam had lower complications than others, and the median length of hospital stay was significantly shorter with proton beam (*15*).

Fang *et al*. reported from MD Anderson Cancer Center, passive proton beam therapy had a low rate of lymphocytopenia during definitive chemoradiotherapy compared with IMRT. Patients underwent proton beam therapy (n = 110) and was matched by propensity score with patients treated with IMRT (n = 110). On multivariate analysis, proton beam therapy had a lower risk of Grade 4 rate of lymphocytopenia (hazard ratio [HR] = 0.5, p = 0.01) than IMRT (*16*). Shiraishi *et al*. from MD Anderson Cancer Center, compared lymphocyte counts on esophageal cancer treated neoadjuvant chemoradiotherapy between passive proton beam therapy and IMRT. Patients' characteristics were matched by propensity score. One hundred thirty-six patients of each group were studied. Radiation dose was 50.4 Gy given in 28 fractions in each group. Grade 4 lymphopenia was significantly less in proton beam therapy compared with IMRT. Proton beam was significantly associated with a reduction in Grade 4 lymphopenia on multivariable analysis. They concluded proton beam therapy prevented Grade 4 lymphopenia during chemoradiotherapy (*17*). Routman *et al*. from Mayo Clinic also reported scanning proton beam reduced Grade 4 lymphopenia during chemoradiotherapy. Seventy-nine and 65 patients were treated with photon and proton beam therapy, respectively. All patients received 41.4 - 50.4 Gy. On multi- and uni-variate analysis they showed proton beam therapy was significantly associated with reduction of Grade 4 lymphopenia (*18*). Lymphopenia is associated with survival of patients with esophageal cancer who underwent chemoradiotherapy (*19*). Lymphocytes are one of the most vulnerable organs to radiation. These results seem to show a dosimetric advantage of proton beam translated into clinical outcome.

Garant *et al*. from Mayo Clinic demonstrated proton beam therapy showed less decline in health-related quality of life (HRQOL) during chemoradiotherapy compared with photon beam therapy. One hundred eighty-nine patients were assessed using the functional assessment of cancer therapy-esophageal (FACT-E) before and after chemoradiotherapy. On multi- and uni-variate analysis proton beam was associated with less decline in FACT-E scores compared with photon beam (*20*).

Clinical data of proton therapy for esophageal cancer

Sugahara *et al*. from University of Tsukuba initially reported clinical results of esophageal cancer treated passive proton beam therapy (*21*) and afterwards Mizumoto *et al*. updated the initial report (*22*). The numbers of clinical stages I, II and III were 8 (15.7%), 23 (45.1%) and 20 (39.2%) patients, respectively. Chemotherapy was not done. Thirty-three patients were treated using photon therapy with median dose of 46 Gy (range 7-60 Gy) followed by proton boost with median dose of 36 Gy (range 7-60 Gy). Total median dose of photon and proton beam was 80 Gy (range 70-90 Gy). Eighteen patients were treated using proton alone with median dose of 79 Gy (range 62-98 Gy). No patients had a treatment interruption due to hematological toxicity. One patient was discontinued because of aspiration pneumonia. Acute toxicity was relatively mild, and six patients had Grade 3 esophagitis. One patient died because of esophageal ulcer. The patients receiving 80 Gy and more had more frequent esophageal ulcer compared with less than 80 Gy. The 5-year overall survival and local control rates for all 51 patients were 21.1% and 38.0%, respectively. The complete response (CR) rates were 100% for patients at the T1 or T2 stage, 77% for T3, and 38% for T4, respectively. Thirty-three percent of patients had recurrence at the primary site. On uni- and multi-variate analysis, prognostic factors for overall survival were only for T stage and that for local control were not identified.

Ishikawa *et al*. reported concurrent chemotherapy

with passive proton beam therapy for 40 patients from University of Tsukuba. The number of clinical stages I, II and III were 16 (40%), 9 (22.5%) and 15 (37.5%) patients, respectively. The dose of 60 Gy was irradiated given in 30 fractions. When residual tumor was observed at 50 Gy by endoscopic examination, an additional dose of 4-10 Gy was boosted. Twenty-one patients had undergone the boost proton beam. Ten and nine patients had Grade 3 or 4 hematological and esophagitis toxicities, respectively. Late Grade 3 toxicities occurred only in two patients. Two patients with T3 disease had stricture of esophagus and ulcer with residual tumor in each. The-3 year overall survival was 70.4%. The 2-year overall survival and local control rates for all was 75.1% and 66.4%, respectively. The clinical CR rates for stage I, II and III were 88%, 89% and 56%, respectively. 56% recurred at the primary site (*23*).

Zeng *et al*. from University of Washington described preliminary results of IMPT for 13 patients with esophageal cancer. All patients underwent neoadjuvant IMPT with a chemotherapy dose of 50.4 Gy given in 28 fractions followed by surgery. Tumor stage and histology were cT3-4 distal esophageal adenocarcinoma. Grade 4 and more toxicity had not occurred during IMPT. Twelve patients underwent surgery after IMPT except one patient because of progression of systemic disease. Of all 12 patients who underwent surgery, pathological CR was seen in 25% and R0 resection was achieved in all patients (*12*).

Lin *et al*. from MD Anderson Cancer Center reported the outcome of 62 patients with esophageal cancer who underwent passive proton beam therapy with dose of 50.4 Gy given in 28 fractions. The numbers of adenocarcinoma and squamous cell carcinoma were 47 (75.8%) and 14 (22.6%), respectively. Most patients were stage II - III disease (84%). Thirty-three (53.2%) and 29 (46.8%) of patients underwent definitive radiotherapy and radiotherapy followed by surgery, respectively. The pathological CR rate was 28%. Proton beam therapy was well tolerated. The rate of Grade 2-3 pneumonitis was 3.2%. The 3-year overall survival and local control rates for definitive radiotherapy were 51.7% and 56.5%, respectively (*24*).

Takeda *et al*. from Southern Tohoku Proton Center reported the results of 47 patients with esophageal cancer treated with photon beam followed by passive proton boost with chemotherapy. The doses of photon and proton were 36 Gy given in 20 fractions and 33-39.6 Gy given in 15-18 fractions, respectively. The number of stages I, II and III were 10 (21.3%), 12 (25.5%) and 25 (53.1%) patients, respectively. None had Grade 4 and more toxicity. One patient (2.1%) had Grade 3 pneumonitis. The 3-year overall survival and local control rates were 59.2%, and 69.8%, respectively (*25*).

Ono *et al*. reported clinical results of 202 patients with esophageal cancer who underwent definitive proton beam therapy from a multicenter in Japan. Seventy-two (35.6%), 30 (14.9%), 52 (25.7%) and 48 (23.8%) patients had clinical stage I, II, III and IV disease, respectively. The median total dose was 87.2 Gy. The 3- and 5-year overall survival rates were 66.7% and 56.3%, respectively. The 5-year overall survival rates for stages I, II, III, and IV were 79.3%, 66.3%, 43.2%, and 28.3%, respectively. The 3- and 5-year local control rates for all were 70.2 and 64.4%, respectively. None had Grade 4 or more toxicities. There was one patient who had Grade 3 pericardial effusion and pneumonia (*26*).

Table 1 shows a summary of clinical outcomes. Interpreting outcomes are difficult due to various doses, stage and type of histology, however a dose over 60 Gy with chemotherapy appear to be superior for overall survival and local control rate for historical photon beam therapy (*27*).

Comparison of clinical outcomes between proton and photon beam therapy

Table 2 shows a comparison of clinical outcomes between proton and photon beam therapy. Xi *et al*. reported survival benefit of passive proton beam therapy retrospectively compared with IMRT from MD Anderson Cancer Center. They compared 343 patients with esophageal cancer who received definitive chemoradiotherapy with proton beam therapy (n = 132) or IMRT (n = 211). The dose was 50.4 Gy given in 28 fractions and the median dose was both 50.4 Gy for the IMRT (41.4-66 Gy) and proton beam therapy (45-63 Gy). The number of clinical stage I/II and III were 117 (34.1%) and 226 (65.9%), respectively. Proton beam therapy had significantly better overall survival (p = 0.011) compared with IMRT. Local control rate was marginal (p = 0.075). Treatment related toxicities were not significant between the two groups. 5-year overall survival for patients with stage III disease was significantly better for proton beam (34.6%) than IMRT (25%) (*28*).

Lin *et al*. prospectively studied total toxicity burden and progression-free survival between proton beam therapy and IMRT in multicenters of the United States of America. Six (5.6%), 41 (38.3%) and 60 (56.1%) had clinical stage I, II and III, respectively. Ninety-five (88.8%) and 89 (83.2%) patients had adenocarcinoma and at a lower location of esophagus, respectively. The dose of proton beam and IMRT was 50.4 Gy given in 28 fractions. One hundred forty-five patients were randomly assigned and 107 patients were evaluated because of an early stopping rule at the interim analysis. The total toxicity burden was 2.3 times higher for IMRT than proton beam therapy. The 3-year progression-free survival (50.8% *vs*. 51.2%) and 3-year overall survival rates (44.5% *vs*. 44.5%) were similar (*29*). Two studies proved dosimetric advantages of proton beam compared with IMRT translated to improved clinical outcomes. These suggest decreased toxicity of proton beam therapy for esophageal cancer may induce prolonged survival

Table 1. Clinical outcome underwent proton beam therapy

Authors (*Ref.*)	Number of patients	Median age (years)	Histology No. (%)	Clinical stage No. (%)	The median dose (Gy)	Type of proton	Chemotherapy	Treatment attitude	Overall survival	Local control rate
Mizumoto *et al.* (*22*)	51	72	Sqcc 50 (98), Malignancy cell 1 (2)	I 8 (15.7), II 23 (45.1), III 20 (39.2)	80 (photon 46, proton 36)	Passive	Not done	Definitive	21.1% (5-year)	38.0% (5-year)
Ishikawa *et al.* (*23*)	40	69	nm	I 16 (40), II 9 (22.5), III 15 (37.5)	60 (plus proton boost 4-10)*	Passive	Concurrent	Definitive	70.4% (3-year)	66.4% (2-year)
Lin *et al.* (*24*)	62	68	Adeno 47 (75.8), Sqcc 14 (22.6)	I 2 (3.2), II 20 (32.3), III 32 (51.6), IV 8 (12.9)	50.4	Passive	Concurrent	Definitive (53.2), Preoperative (46.8)	51.7% (3-year)	56.5% (3-year)
Takeda *et al.* (*25*)	47	63	Adeno 1 (2.1), Sqcc 46 (97.9)	I 10 (21.3), II 12 (25.5), III 25 (53.1)	73.4 (photon 37.4, Proton 36)	Passive	Concurrent	Definitive	59.2% (3-year)	69.8% (3-year)
Ono *et al.* (*26*)	202	69	Adeno 7 (3.5), Sqcc 195 (96.5)	I 72 (35.6), II 30 (14.9), III 52 (25.7), IV 48 (23.8)	87.2 (58.9% used photon)	Passive	Concurrent (75.8)	Definitive	56.3% (5-year)	64.4% (5-year)

*52% of patients underwent proton beam boost. Adeno denotes adenocarcinoma, Sqcc denotes squamous cell carcinoma, nm denotes not mentioned, Percentage in parentheses.

Table 2. Comparison of proton beam therapy and IMRT for clinical outcomes

Authors (*Ref.*)	Study manner	Number of patients	Median age (years)	Radiation source	Histology No. (%)	Clinical stage No. (%)	Median dose (Gy)	Overall survival	Progression-free survival	Toxicity
Xi *et al.* (*28*)	Retrospective	132	67	Proton (94.7% passive scattering)	Adeno 90 (68.2), Sqcc 42 (31.8)	I/II 47 (35.6), III 85 (64.4)	50.4	Stage III 34.6% (5-year) $p = 0.038$*	33.5% (5-year) $p = 0.005$	37.9% (Grade 3 or 4)n.s.
		211		IMRT	Adeno 155 (73.5), Sqcc 56 (26.5)	I/II 70 (33.2), III 141 (66.8)	50.4	Stage III 25%	13.2%	45.0% (Grade 3 or 4)
Lin *et al.* (*29*)	Prospective	46	67	Proton (80% passive scattering)	Adeno 42 (91.3), Sqcc 4 (8.7)	I 2(4.3), II 17(37), III 27 (58.7)	50.4	50.8% (3-year)n.s.	44.5% (3-year)n.s.	17.4% $p = 0.018$
		61	67	IMRT	Adeno 53 (86.9), Sqcc 8 (13.1)	I 4(6.6), II 24(39.3), III 33 (54.1)	50.4	51.2%	44.5%	39.9%

*Stage I/II were not significant, n.s.denotes not significant. Adeno denotes adenocarcinoma. Sqcc denotes squamous carcinoma. IMRT denotes intensity modulated radiotherapy, Percentage in parentheses.

and possible dose escalation without increasing toxicity.

Future directions

The standard dose of concurrent chemoradiotherapy for locally advanced esophageal cancer is 50.4 Gy given in 28 fractions, which was determined by the radiation therapy oncology group (RTOG) 94-04/INT 0123 trial (*27*). A higher dose of 64.8 Gy given in 36 fractions was expected to improve overall survival, however overall survival of a higher dose group at 2-years was lower than the lower dose of 50.4 Gy given in 28 fractions. Treatment-related deaths were higher in the high dose group than the lower group, which affected survival of the high dose group (*27*). If treatment-related effects could be reduced by proton beam, overall survival could possibly improve.

Several dose escalating studies were reported using photon beam. Welsh *et al*. reported the results of a phase I/II trial from MD Anderson Center. Foyty-four patients underwent chemoradiotherapy with a simultaneous integrated boost (SIB) of 58.8 to 63 Gy. Local control rate at 1-year was 69.9%. They concluded that dose-escalation may improve local control (*30*). Yu *et al*. reported 45 patients underwent 63 Gy with SIB. Local control rates were 83.3 % at 1-year and 67.5% at 3-years (*31*). Finally, Luo *et al*. reported the result of meta-analysis for the effect of modern high-dose compared with standard dose photon therapy. They showed high dose improved overall survival (HR = 0.78, $p < 0.001$) and concluded high dose based on modern radiotherapy appears to improve overall survival (*32*).

Mizumoto *et al*. reported results of concomitant proton boost combined with photon therapy. Nineteen patients underwent this hyper-fractionated radiotherapy. Total irradiated dose ranged from 74 Gy to 80 Gy. Seventeen (89%) patients achieved CR. The 1- and 5-year local control rates for all 19 patients were 93.8% and 84.4 %, respectively (*33*). It is necessary for radiation oncology to prove improvement of survival not only reduced toxicity. In 2008, Suit *et al*. reported data of much value to radiation oncology to determine the clinical consequence of changes in dose, and dose fractionation (*34*). Based on a photon dose escalation study and results of proton therapy, dose escalation may improve survival for esophageal cancer. A phase I study of dose escalation proton beam therapy has been activated at the University of Pennsylvania.

A phase III randomized trial (NRG-GI006) comparing proton beam therapy versus IMRT has been started (*35*). The primary endpoint is non-inferior overall survival with proton beam therapy compared with IMRT and less than Grade 3 and more cardiopulmonary toxicity. The dose of 50.4 Gy given in 28 fractions with chemotherapy is irradiated in esophageal cancer in two groups. An active scanning proton center is increased in the United States of America, so active scanning expects much lower toxicities than passive scattering in this trial.

Some passive proton beam center, with a wide area (25 × 25 cm) is difficult to irradiate, so proton beam is used as a boost after photon therapy. Many clinical reports from Japan included combined photon and passive scattering proton beam therapy. Passive scattering proton has a high dose in front of the tumor and does not irradiate the entire esophagus. In the dosimetric plan analysis, a scanning proton plan was superior to a scattering plan. Scanning proton beam therapy may provide the original property of proton beam in the clinic.

High cost is a great criticism for proton beam therapy. Fortunately, cost is gradually deceasing, however, large space and a high running cost is needed to generate high energy proton beam. In Japan, the cost of esophageal cancer undergoing proton beam therapy is three times higher than IMRT. This is one of the reasons randomized trials are lacking. Laser accelerated proton beam, which has a unique niche is now under development (*36*). Laser accelerated protons do not use a synchrotron or cyclotron, so space and running cost is low. Laser accelerated protons are relatively low energy with wide energy, and low reproducibility. After these problems are resolved, laser accelerated proton beam therapy may spread widely just as the linear accelerator replaced Cobalt-60 (^{60}Co). If proton beam therapy has low cost, many patients will receive proton beam therapy and clinical trials will be enhanced.

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Surgical treatment for oral tongue squamous cell carcinoma: A retrospective study of 432 patients

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Abstract: The incidence of oral cancer in Japan accounts for 1% of all cancers, with oral tongue cancer accounting for 60% of oral cancers based on the subsite. The most common histologic type is squamous cell carcinoma. This study aimed to evaluate the series of surgical treatments for 432 patients with oral tongue squamous cell carcinoma (OTSCC). Initial surgical treatments for the primary site included partial glossectomy, hemiglossectomy, and total or subtotal glossectomy in 348, 58, and 26 patients, respectively. Therapeutic neck dissection, elective neck dissection, and subsequent neck dissection were performed in 74, 53, and 37 patients, respectively. Patients with advanced cases had level IIb, IV, and V metastasis and outside regional lymph node metastases. The cumulative 5-year disease-specific survival rate for OTSCC was 92.8%, and the rates for each stage were 96.6%, 93.9%, 84.1%, and 79.0% in stages I, II, III, and IV, respectively. The recurrence rate, overall salvage rate for recurrent cases, and rate for the additional surgical group were 10.4%, 46.7%, and 78.6%, respectively. Patients with multiple cervical lymph node metastases, extranodal extension, metastases to multiple levels, and lower neck metastases had poor prognosis. In conclusion, careful follow-up is necessary to detect recurrence of primary tumors at a stage when surgical treatment can be performed, and cervical lymph node status is one of the most important prognostic factors in OTSCC.

***Keywords*:** oral cancer, oral tongue squamous cell carcinoma (OTSCC), surgical treatment, neck dissection

Introduction

Annually, approximately 300,000 people worldwide develop oral cancer (*1*). The majority of oral malignancies arise from epithelial tissue, and squamous cell carcinoma is the predominant tumor type (*2*). The most common subsite of oral squamous cell carcinoma (OSCC) in Japan is the oral tongue, and the estimated frequency of oral tongue squamous cell carcinoma (OTSCC) is 60% (*3*). Although the oral tongue can be inspected directly, it is often diagnosed in its advanced stages. The oral tongue controls functions such as mastication, taste, articulation, and deglutition; hence, the treatment of OTSCC has a great impact on the postoperative dysfunction as well as life prognosis. Despite advances in diagnostics and therapeutic techniques, the survival rate of OSCC has only improved by 5% in the past 20 years, and the 5-year survival rate of OSCC is 60% (*4*).

Few reports have examined the course of treatment and prognosis in patients with OTSCC. This study aimed to evaluate the series of treatments for OTSCC and their outcomes in a single institution.

Patients and Methods

Between January 2008 and December 2017, 778 patients with OSCC underwent radical surgical treatment at the Department of Oral and Maxillofacial Surgery of the Tokyo Medical and Dental University (Tokyo, Japan). Among these patients, 432 (55.5%) had OTSCC. The observation period was set from the date of treatment initiation to December 31, 2019, and the mean follow-up period was 70.5 months (range, 1.6-141.4 months). Patients with multiple oral cancers and treated with brachytherapy were excluded. Clinicopathological information including age, sex, TNM classification (Union for International Cancer Control 7th edition), treatment, and outcomes were obtained from medical charts. Speech intelligibility was assessed using a hundred monosyllable Japanese speech intelligibility test (*5*), and each patient read all items on the list twice. Five independent listeners scored speech intelligibility, and the mean scores of three of these listeners (excluding the highest and lowest scores) were used as a measure of speech intelligibility.

Survival curves were estimated according to the

Kaplan-Meier method, and differences were examined using the log-rank test. The analyses were performed using PASW Statistics version 25 (SPSS Inc., Chicago, IL, USA).

This study was conducted following the Declaration of Helsinki and was approved by the ethics committee of the Tokyo Medical and Dental University, Faculty of Dentistry (No. D2015-600).

Results

Initial treatment for primary site and neck

There were 264 males and 168 females among the 432 patients, and the mean age was 57.8 years (range, 21-86 years). Among both males and females, the highest number of patients were in their 60s (65 and 38 patients, respectively). Tumor clinical stages were stage I in 235 patients, stage II in 108 patients, stage III in 40 patients, and stage IVA in 49 patients (Table 1).

Table 1. Characteristics of patients

Variables	Patients
Sex	
Male	264
Female	168
Age years (mean)	21-86 (57.8)
Stage	
I	235
II	108
III	40
IVA	49
Treatment for primary	
Surgical only	360
Adjuvant therapy	36
Neoadjuvant therapy	17
Adjuvant and neoadjuvant therapy	19
Neck dissection	
Therapeutic neck dissection	74
Elective neck dissection	53
Subsequent neck dissection	37
Type of recurrence	
Local recurrence	17
Regional recurrence	22
Locoregional recurrence	6

The initial treatment for the primary cancer consisted of surgery alone in 360 patients, adjuvant therapy in 36 patients, neoadjuvant therapy in 17 patients, and adjuvant and neoadjuvant therapy in 19 patients (Table 1). Neoadjuvant therapy consisted of chemotherapy in 16 patients and chemoradiotherapy in 20 patients. As for adjuvant therapy, 11 patients received chemotherapy, 14 patients received radiotherapy, and 30 patients received chemoradiotherapy.

Initial surgical treatment for the primary site consisted of partial glossectomy in 348 patients, hemiglossectomy in 58 patients, and total or subtotal glossectomy in 26 patients. We performed combined adjacent tissue resection for 18 patients in the hemiglossectomy group (combined marginal mandibulectomy in 5 patients, lateral pharyngectomy in 11 patients, and both in 2 patients) and 14 patients in the total or subtotal glossectomy group (combined marginal mandibulectomy in 6 patients, lateral pharyngectomy in 4 patients, and both in 4 patients). Table 2 shows the reconstruction type of the primary site. Primary closure was the most common type in the partial glossectomy group (82.8%), radial forearm flap in the hemiglossectomy group (84.5%), and rectus abdominis myocutaneous flap in the total or subtotal glossectomy group (65.4%).

Six patients had histopathologically positive margins on the surgical specimen of the primary tumor, 5 patients underwent additional resections, and 1 patient received chemoradiotherapy. None of the patients had local recurrence.

Neck dissection was performed in 127 patients as the initial treatment. In these patients, 74 underwent therapeutic neck dissection (62 unilateral, 12 bilateral) and 53 underwent elective neck dissection (Table 1). Among patients who underwent therapeutic neck dissection, 61 (82.4%) had cervical lymph node metastases identified pathologically; in contrast, among those who underwent elective neck dissection, 13 patients (24.5%) had cervical lymph node metastases. Thirty-nine patients, excluding 2 patients who had primary recurrence, developed subsequent cervical lymph node

Table 2. Initial treatment of primary site and reconstruction

Variables	Partial glossectomy (n = 348)		Hemiglossectomy (n = 58)		Total or subtotal glossectomy (n = 26)	
Primary closure	288	(82.8%)	-	(0%)	-	(0%)
STSG	15	(4.3%)	1	(1.7%)	-	(0%)
PGA sheet	16	(4.6%)	1	(1.7%)	-	(0%)
Artificial dermis	2	(0.6%)	-	(0%)	-	(0%)
RF flap	27	(7.8%)	49	(84.5%)	4	(15.4%)
ALT flap	-	(0%)	2	(3.4%)	2	(7.7%)
TFL flap	-	(0%)	1	(1.7%)	3	(11.5%)
RA flap	-	(0%)	3	(5.2%)	17	(65.4%)
LDMC and scapular flap	-	(0%)	1	(1.7%)	-	(0%)

ALT: anterolateral thigh; LDMC: lattissimus dorsi musculocutaneous; PGA: polyglycolic acid; RA: rectus abdominis myocutaneous; RF: radial forearm; STSG: split thickess skin graft; TFL: tensor fasciae latae.

Table 3. Level of metastatic lymph nodes (*n* = 111)

Level	Ipsilateral		Contralateral	
Ia	16	(14.4%)	3	(2.7%)
Ib	46	(41.4%)	8	(7.2%)
IIa	79	(71.2%)	3	(2.7%)
IIb	4	(3.6%)	-	(0%)
III	39	(35.1%)	4	(3.6%)
IV	9	(8.1%)	1	(0.9%)
V	3	(2.7%)	-	(0%)
Others	15	(13.5%)	-	(0%)

metastases. The mean duration of metastases, which appeared clinically was 8.5 months (range, 0.7-32.9 months). In these patients, 37 underwent therapeutic neck dissection and the other 2 were treated in other institutions. Among the 37 patients, 12 were treated with adjuvant therapy.

Among the 164 patients who underwent neck dissection, 111 had histopathological lymph node metastases. Of these, 94 patients had unilateral neck dissection and 17 patients had bilateral neck dissection. The patterns of cervical lymph node metastases are shown in Table 3. In the ipsilateral site, level IIa was the most common (71.2%), while level Ib was the most common in the contralateral site (7.2%). There was a low frequency of metastases to the ipsilateral levels IIb (3.6%), IV (8.1%), and V (2.7%), and were found in only 13 patients. The mean number of metastatic lymph nodes in patients with levels IIb, IV, and V regional metastases was 10.5 (range, 3-28), and 5 out of 13 patients developed distant metastases. Skip metastasis to level III, without involvement of levels I or II, was confirmed in 9 patients (8.1%). Metastases outside the regional lymph nodes were observed in 15 patients. Thirteen patients had metastasis to the lingual nodes, while there was one patient each who had metastasis to the intraglandular parotid nodes and paratracheal nodes. Lastly, 8 out of 15 patients developed distant metastases.

Recurrence and salvage treatment

Seventeen patients had local recurrences, 22 had regional recurrences, and 6 had locoregional recurrences. The recurrence rate of OTSCC was 10.4%. In local recurrences, 11 patients underwent additional surgical treatment and 10 patients were salvaged. Conversely, in the 6 patients who received chemotherapy and/or radiotherapy, only 2 survived. In regional recurrence, 17 patients had recurrence beyond the dissected field. Sixteen patients underwent surgery, of which 11 were salvageable. Six patients who received chemotherapy and/or radiotherapy had unfavorable outcomes. In locoregional recurrence, only one patient could be salvaged with neck surgery and proton radiation therapy to the primary recurrent tumor. The overall salvage rate for recurrent cases was 46.7%, and the rate for the additional surgical group was 78.6%. Distant metastases were found in 19 patients (4.4%), 9 of which gained locoregional control.

Postoperative function

The speech intelligibility test was performed in 296 patients (68.5%), and the mean period from surgery to speech evaluation was 21.6 days (range, 3-143 days). The mean scores were 92.9% (range, 41.0-100%) in the partial glossectomy group (*n* = 216), 79.1% (range, 32.7-97.3%) in the hemiglossectomy group (*n* = 55), and 49.0 % (range, 24.3-83.3%) in the total or subtotal glossectomy group (*n* = 25).

The mean time from initial surgery to oral food intake was 6.0 days (range, 0-27 days) in the partial glossectomy group, 22.0 days (range, 6-92 days) in the hemiglossectomy group, and 29.2 days (range, 14-127 days) in the total or subtotal glossectomy group, excluding 4 patients who were fed *via* percutaneous endoscopic gastrostomy (PEG). The four patients who underwent PEG consisted of 2 patients with hemiglossectomy, 1 patient with subtotal glossectomy, and 1 patient with total glossectomy.

Outcomes of surgical treatment of OTSCC

The cumulative 5-year overall survival and disease-specific survival (DSS) rates for OTSCC were 91.1% and 92.8%, respectively. The rate of DSS for each stage was 96.6% in stage I, 93.9% in stage II, 84.1% in stage III, and 79.0% in stage IV (Figure 1). The rate of DSS with cervical lymph node metastases was 76.6% (*n* = 111) and 98.2% in negative lymph nodes metastasis (*n* = 321) ($p < 0.01$) (Figure 2). DSS rates were also calculated for the metastatic pattern of the cervical lymph nodes. The rates for single and multiple lymph node metastases were 89.9% (*n* = 47) and 66.9% (*n* = 64) ($p = 0.013$), with and without extranodal extension were 68.1% (*n* = 59) and 85.2% (*n* = 52) ($p = 0.011$), single and multiple levels of metastases were 89.1%

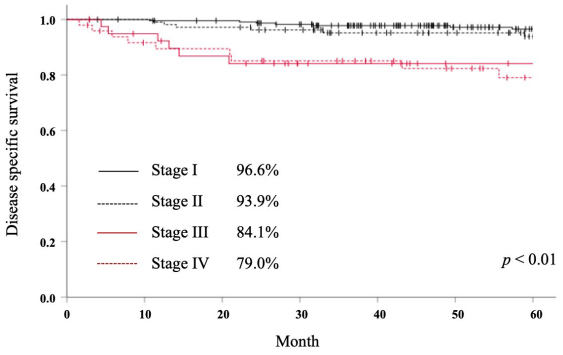

Figure 1. Kaplan-Meier estimates of disease-specific survival (DSS) among patients with oral tongue squamous cell carcinoma (OTSCC) according to the tumor clinical stage.

(n = 62) and 60.3% (n = 49) (p = 0.002), and with and without lower neck involvement (level IV and/or V) were 42.4% (n = 11) and 80.4% (n = 100) (p = 0.005), respectively (Figure 3).

Discussion

The morbidity of oral cancers and the frequency of occurrence by subsite vary by country, race, and lifestyle. The incidence of oral cancer in Japan is reported to be 1% of all cancers, and the number of patients is increasing with the age of the population (*4*). In Western countries, the number of patients with oral cancer among young people and nonsmokers is on the rise (*6*), but no such trend has been observed in Japan.

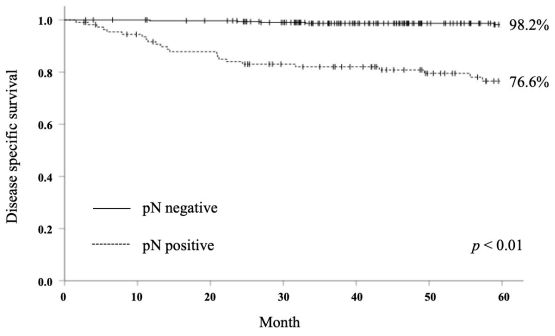

Figure 2. Kaplan-Meier estimates of disease-specific survival (DSS) among patients according to the presence or absence of the cervical lymph node metastasis.

Surgical resection of the oral tongue impairs its primary functions such as articulation, mastication, and swallowing. In partial glossectomy or hemiglossectomy resection cases, it is desirable to reconstruct the tongue without impairing the function of the remaining tongue. In total or subtotal resection cases, on the other hand, it is desirable to reduce the space between the reconstructed tongue and the palate to restore articulation and swallowing functions (*3*). For this reason, the radial forearm flap is often used in patients with hemiglossectomy of the tongue (*7*) and the rectus abdominis myocutaneous flap is used in patients with total or subtotal resection of the tongue (*8*). Our strategy of reconstruction according to the extent of resection was similar to these results.

As an assessment of function after tongue resection and reconstruction, we tested for articulatory function. It is clear from the present study that as the extent of resection increases, articulatory function declines. Similarly, the time until initiation of oral food intake varies with the extent of resection. At our facility, the swallowing function is assessed postoperatively by video fluoroscopy, and indirect training, direct training, and use of palatal augmentation prosthesis are performed as needed. This allows most patients to eat through the oral route before they leave the hospital. In addition to the type of flap, the design of the flap and the method should be considered to achieve good postoperative oral function. In reconstruction of a large excision of the tongue, a protuberant shape is useful

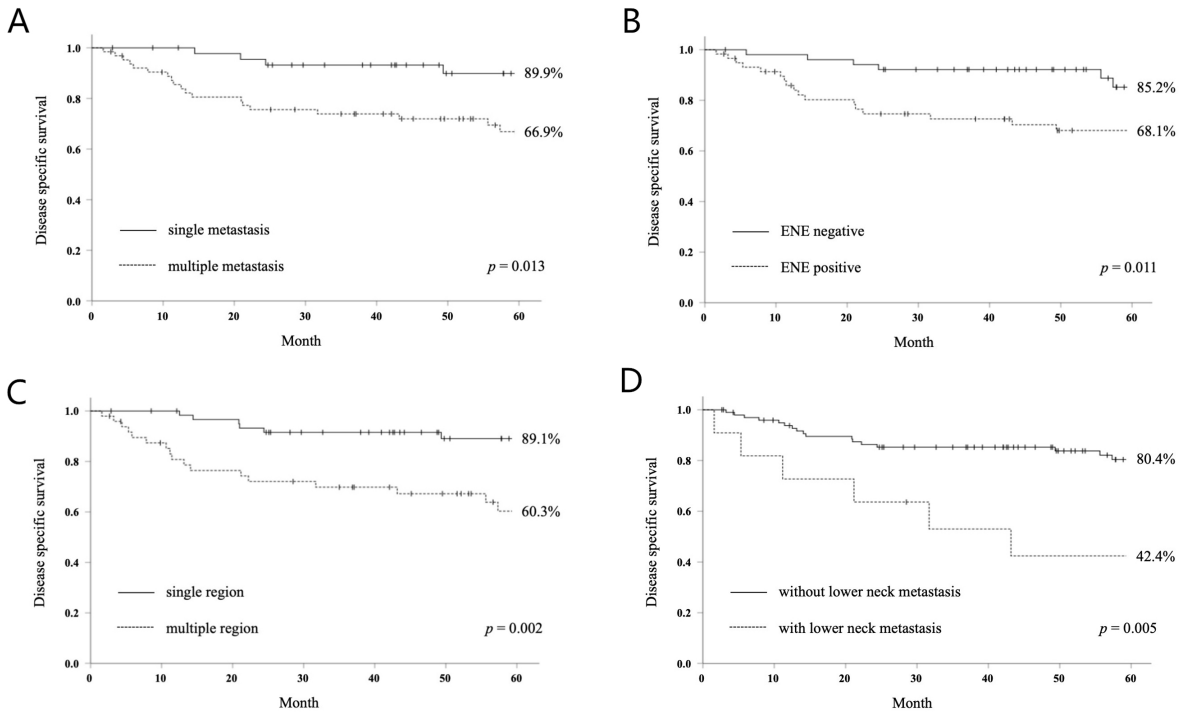

Figure 3. Kaplan-Meier estimates of disease-specific survival (DSS) among patients according to the metastatic pattern of the cervical lymph nodes. (A) Single and multiple lymph node metastasis. **(B)** With and without extranodal extension. **(C)** Single and multiple levels of metastasis. **(D)** With and without lower neck (level IV and/or V) metastasis.

in preserving swallowing and articulation function after surgery (*9,10*), and laryngeal suspension is also performed to prevent subsidence of the reconstructed tongue (*11*).

There is a lack of consensus regarding elective neck dissection. Although the metastasis rate of patients undergoing elective neck dissection in this study was 24.5%, the metastatic rate in early stage cancers is unknown because our institution performs elective neck dissection in cases of locally advanced cancer that require free flap reconstruction. Even after elective neck dissection, cervical recurrence can occur (*12*), and further studies on the indications for elective neck dissection, the extent of dissection, postoperative treatment, and follow-up are needed. Cervical lymph node metastasis in oral cancer was more common in levels I and II (*13*), which was also the case in the present study, metastasis to regions with low frequency of lymph node metastasis, such as level IIb, IV, and V, tended to show distant metastases. Risk factors involved in neck failure include multiple cervical lymph node metastases, extranodal extension, metastases to multiple levels, and lower neck metastases (*14,15*). In the present study, significant differences were found for all factors; however, the analysis of poor prognostic factors in this study included both patients who received adjuvant therapy and those who did not. Adjuvant therapy is often administered to patients who have poor prognostic factors, and it is assumed that there are some factors that cannot be controlled even with adjuvant therapy; hence, future research should focus on resistance to adjuvant therapy.

Surgery is generally the treatment of choice for recurrent cancer because it offers a better prognosis than other therapies if the cancer is resectable (*16*). We surgically treated 28 out of 45 patients with recurrence and 22 had favorable outcomes. In contrast, the prognosis for unresectable recurrent tumors is poor, with a low survival rate. It is more important to detect recurrence when surgical treatment is possible. At our institution, CT or PET/CT are routinely performed once or twice a year for at least 2 years after primary treatment or neck dissection.

In recent years, comprehensive analyses of gene mutations in head and neck squamous cell carcinoma (HNSCC) including OSCC have also been conducted, revealing substantial information about the genomic alterations in HNSCC (*17*). We also reported that receptor tyrosine kinase amplification or co-expression of EGFR and MET was associated with poor prognosis (*18,19*). However, these findings have not yet been translated into clinical applications. Further research is needed to explore biomarkers for treatment tolerance and prognosis prediction, and their clinical applications to implement precise medical care by stratifying patients in oral cancer.

In conclusion, careful follow-up is necessary to detect recurrent primary tumors at a stage when surgical treatment can still be performed. Tumor cells in OTSCC often metastasize to cervical lymph node levels Ia and IIa. However, metastasis to level IIb and the lower cervical region was also found in patients with multiple metastases, and occult metastases were found in locally advanced cases. Cervical lymph node status is one of the most important prognostic factors in OTSCC. Finally, further studies regarding treatment strategies are needed in the future.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Determining desire to live among patients with advanced hepatobiliary-pancreatic cancer for whom curative treatment is not indicated

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Abstract: This study aimed to evaluate the desire to live among patients with advanced hepatobiliary-pancreatic cancer who were excluded from radical treatment and to examine the ideal nursing support for them. We recruited 18 patients in a department specializing in the treatment of hepatobiliary-pancreatic cancer at a university hospital in the metropolitan area of Japan. We included those with advanced hepatobiliary-pancreatic cancer who received a treatment other than definitive treatment. We conducted semi-structured interviews, and the responses were analyzed qualitatively and descriptively. Events experienced by patients with advanced hepatobiliary-pancreatic cancer and out of indication for radical treatment were divided into five major phases, while desire to live was divided into 11 categories. Two of these categories were represented by the word "death". The desire to live was present in all phases, and the expressions of these desires were diverse. Patients suppressed expressing their desire to live because they understood that their situation was challenging. In addition, there was a tendency to avoid expressing their desire to live to medical staff and their families. We found that nurses need to establish a medical relationship in which patients can express their desire to live and become connected to nursing support.

***Keywords*:** advanced cancer, well-being, nursing support, chemotherapy, intractable cancer

Introduction

Hepatobiliary and pancreatic cancer are subjected to poor prognosis because the number of morbidities and deaths are almost equal. In Japan, the five-year relative survival rate for regional lymph node metastases and invasion of adjacent organs is 3.5% for liver cancer, 1.9% for biliary tract cancer, and 1.3% for pancreatic cancer (*1*), which is extremely low when compared to other forms of cancer. One of the many factors attributed to these percentages is an extremely high recurrence rate even after radical surgical resection (*2-4*). In addition, biliary-pancreatic cancer and non-viral liver cancer are difficult to detect at an early stage. Hepatitis-derived hepatocellular carcinoma may be associated with cirrhosis and markedly impaired liver function, making some patients ineligible for surgical resection and making radical cure difficult (*5-7*). Chemotherapy, which is administered when surgical resection or effective local therapy (*i.e.*, radiofrequency ablation [RFA] or transcatheter arterial chemoembolization [TACE]) is unavailable, has very few drug options and a poor response rate (*2,8,9-11*). Advanced hepatobiliary-pancreatic cancer is generally treated as an intractable form of cancer.

Since hepatobiliary-pancreatic cancer progresses asymptomatically, most patients are diagnosed with an advanced stage of cancer. Consequently, patients are deeply shocked by the sudden diagnosis (*12*) and experience a high proportion of psychological distress during treatment (*13-15*). In addition, patients with hepatobiliary-pancreatic cancer show more depressive symptoms (*16,17*) and experience a lower quality of life than healthy people and patients diagnosed with other forms of cancer (*18,19*). When advanced hepatobiliary-pancreatic cancer is beyond the scope of curative treatment, not only are treatment options limited, but there is also uncertainty about the continuity of treatment. Therefore, it is commonly presumed that patients will experience an immense psychosocial burden.

In Japan, a previous study (*20*) reported the various implications regarding the feelings of patients with advanced cancer who wish to continue treatment knowing that they cannot be cured. It was found that these patients have a strong desire to live and hold positive expectations for treatment. Some qualitative studies have reported the experiences of patients under treatment for an advanced stage of cancer, in which patients expressed "I want to stay alive" (*21,22*). For patients with intractable cancer, receiving treatment is the only hope (*23*). Moreover, they are more eager to survive

in the face of the side effects of treatment and endure them (*24*). It is presumed that patients with advanced hepatobiliary-pancreatic cancer, who are excluded from curative treatment, want to stay alive with standard treatment, despite knowing they are incurable. However, few studies have focused on the implications of these patients' desire to live.

In this study, we clarify how patients with advanced hepatobiliary-pancreatic cancer who are not indicated for curative treatment continue to feel the desire to live, based on the events they experience during the treatment process. By doing so, we will deepen the understanding of patients and consider the role of nursing support.

Methods

Study design

Qualitative research has been used by psychologists and sociologists since the early 20th century. The life events that humans experience are interdependent and form complex fabrics (*25*). A narrative refers to the making of meaning through personal experience by way of reflection, in which storytelling is a key element, and metaphors and folk knowledge take what place (*26*).

This study evaluates patients diagnosed with advanced hepatobiliary-pancreatic cancer, a rare form of intractable cancer, not identified for curative treatment. To investigate such rare phenomenon, it can be challenging to secure a sample large enough to achieve the representativeness and generalization required for survey research. Additionally, to understand the complexity of the patient's experience, it is necessary to be in their proximity to gain insight. Therefore, it was appropriate to use qualitative research for this study.

Definition of terms

"*Desire to live*": With reference to research by Morishita *et al.* (*20*), we defined desire to live as the desire of patients with advanced hepatobiliary-pancreatic cancer to continue receiving standard treatment despite their poor prognosis and absence of a curative treatment. There are individual differences in their expression of the desire to live such as "want to stay in the world" or "do not want to die".

"*Standard treatment for advanced hepatobiliary-pancreatic cancer that has been excluded from curative treatment*": Standard treatment is a method specified in the treatment algorithm of clinical practice guidelines created by the Japanese Society of Hepatology, Japan Pancreas Society, and the Society of Hepatobiliary and Pancreatic Surgery, most of which have adopted chemotherapy and radiation therapy. Recently, a large study in Japan has shown that survival rate of RFA is equivalent to that of surgical resection (*27*). In addition, TACE has been reported to improve prognosis (*3*), so we decided to exclude RFA and TACE for liver cancer.

Recruitment of the participants

The participants of this study consisted of patients visiting the oncology department of a university hospital in the Tokyo metropolitan area. The selection criteria were as follows: a formal diagnosis of advanced hepatobiliary-pancreatic cancer, receiving chemotherapy or radiation therapy beyond the indication of a curative treatment, aged between 20 and 80 years, and having a performance status of 0 to 2. Moreover, we excluded those who had difficulty communicating, a mental illness or cognitive problems, and serious complications such as cancer or heart conditions.

Data collection and procedure

The data were collected from March 2017 to August 2018. We asked the doctors who cooperated in this study to select eligible patients and provide them with an overview of the research during outpatient treatment. We offered a more detailed explanation to patients interested in the study.

To collect the data, we developed a semi-structured interview guide to include processes ranging from detecting cancer to ongoing treatment, changes in physical and psychological conditions, and relationships with healthcare providers (Table 1).

The interview time was limited to 40 minutes. However, where additional data were required, interviews were conducted multiple times with patients' approval. In addition, as complementary data for the interview, we observed patients' appearance during outpatient visits and hospitalization.

Data analysis

The data were analyzed qualitatively (*25*). First, we read the recorded data thoroughly and carefully, focusing on the statements that expressed patients' desire to live, and coded each statement. Second, we combined similar codes to generate subcategories. By considering the differences and similarities in the subcategories, we weighed the time course of the events experienced by the participants, finally integrating them into the categories. We then created a structural diagram with categories arranged to visualize the transition of patients' desire to live.

To ensure reliability, we conducted participant observations for nearly 20 months and continuously compared the data directly obtained from the participants. We also had regular discussions with nurses and researchers involved in cancer treatment (*26*). This entire process was supervised by a qualitative research expert who confirmed the validity of the analyses.

Table 1. Semi-structured interview guide

Outline	Interview question
Process from detection of cancer to treatment	Please tell us about your work and daily life before your diagnosis. What did the doctor tell you? How did you feel about the diagnosis and treatment? Why did you decide to have treatment?
Changes in physical condition	How have you changed physically since you started treatment? How do your symptoms affect your daily life? How do your symptoms affect your feelings? What do you do about your symptoms?
Changes in psychological condition	How has your psychology changed since diagnosis and the start of treatment? Do you have any concerns? When do you feel positive/negative? How do you cope with difficult times?
Relationships with healthcare providers	What do you discuss with your healthcare provider? What has been your most memorable experience of working with healthcare professionals? What are your requirements for medical care and staff?

Table 2. Participants' characteristics

ID	Gender	Age	Diagnosis	surgical history	Month of chemotherapy	Employment status
A	Female	50	Recurrence of pancreatic cancer	surgical resection	1	Employed
B	Male	50	Pancreatic cancer with hepatic artery infiltration	none	16	Employed
C	Male	50	Pancreatic cancer with liver metastasis	none	3	Employed
D	Male	50	Pancreatic cancer with liver metastasis	none	17	Medical leave
E	Female	50	Bile duct cancer Lymph node metastasis	none	3	Unemployed
F	Female	50	Bile duct cancer with liver metastasis	none	3	Employed
G	Female	60	Pancreatic cancer with liver metastasis, peritoneal dissemination	none	12	Unemployed
H	Female	70	Pancreatic cancer and lung cancer (double cancer)	none	28	Unemployed
I	Female	70	Recurrence of pancreatic cancer	surgical resection	17	Unemployed
J	Male	70	Pancreatic cancer with hepatic artery infiltration	none	15	Retired
K	Female	70	Recurrence of hepatocellular carcinoma	surgical resection	2	Unemployed
L	Male	70	Recurrence of hepatocellular carcinoma	surgical resection	2	Retired
M	Male	70	Recurrence of hepatocellular carcinoma	surgical resection	24	Retired
N	Female	70	Pancreatic cancer with hepatic artery infiltration	none	1	Unemployed
O	Male	70	Pancreatic cancer with hepatic artery infiltration	none	4	Employed
P	Female	70	Pancreatic cancer with lymph node metastasis	none	1	Unemployed
Q	Female	70	Pancreatic cancer	none	5	Unemployed
R	Female	80	Gallbladder cancer with lymph node metastasis	none	5	Unemployed

Ethical considerations

We used the research explanation document to inform participants about the purpose and methods of this study, their free will to participate and withdraw from the research, protection of their personal information, and disclosure of research results. Subsequently, participants gave their consent in writing.

We surveyed in a private room where participants could maintain confidentiality and confirm the stability of their physical condition and side effects before and after the interview. This study was conducted in accordance with the Declaration of Helsinki principles and approved by the Ethics Review Committee of the National Center for Global Health and Medicine (approval number: NCGM-G-002109-00), the Ethical Review Committee of the Faculty of Medicine, and the Faculty of Health Sciences attached to the institution where the research was carried out (approval number H28-166 and 902).

Results

Participants' characteristics

During the survey period, 18 patients, 7 males (38.9%) and 11 females (61.1%), received a referral from a doctor and provided their consent to participate (Table 2). The average age of participants was 67.2 (± 10.2) years. Regarding the types of carcinomas detected, 3 (16.7%) participants had liver cancer, 12 (66.6%) had pancreatic cancer, and 3 (16.7%) had gallbladder and bile duct cancer; most of them had distant metastases. Either RFA or TACE was performed previously on 13 (72.2%) participants who had already opted out of radical treatment at first onset and 5 (27.8%) who relapsed after surgical resection. All participants were receiving

chemotherapy for an average duration of 8.8 (± 8.6) months. Interviews were conducted one to three times per person. In total, there were 27 interviews, which took 1,242 minutes.

Patients with advanced hepatobiliary-pancreatic cancer who were no longer eligible for radical treatment and wanted to live

The analyses led to identifying 11 categories, of which 2 were represented by the word "death", a thought-provoking word meant to cause reflection on the termination of life. We observed that such paradoxical expressions of life underlie the desire to live. Events experienced by patients with advanced hepatobiliary-pancreatic cancer who were out of indication for radical treatment were classified into five major phases: "Cancer detection", "Receipt of diagnosis/notification", "Seeking a place to receive treatment", "Receipt of treatment", and "Uneven therapeutic effect".

Belief that the disease was curable

Participants were made aware of their physical condition through medical examinations and subjective symptoms. Those who presented no history of drinking, smoking, or problems in their medical examination six months prior did not consider the abnormalities significant. They reported that in the few days before their definitive diagnosis, living was "matter-of-fact". Therefore, participants strongly believed that they could be discharged or return to their healthy selves when the symptoms subsided. One such participant stated, "When I was admitted to the hospital because of jaundice, I thought I would have to cure only that. I didn't think it was a rainy day". (ID: M)

Everything is overshadowed by death

During cancer treatment, participants received three notifications. The first informed them of their refractory and progressive disease, the second was that Stage IV was already unresectable, and finally that the treatment was limited. In addition, some doctors affirmed life expectancy. Some participants who had suffered from another type of cancer and overcame it perceived this multiple announcement method to be different from their past experiences. Both new and recurrent patients were unwilling to accept the information and reported that it did not feel real. In particular, new patients said they had no hope of living or were about to give up on living. In fact, one of them reported, "Until the treatment started, I felt like I was dead. On my way to work, the people I passed by looked so energetic that it was very painful. I am still very lonely". (ID: A)

Cannot die yet

Despite being aware that they would most likely die, participants sought treatment because of the importance they gave to their parents, children, and spouses; they prioritized their families over themselves. Some participants stated that they could not afford to die because they had children with illnesses or disabilities, while others in their 70s and older, caring for their parents and grandchildren, reported the same feeling. One of them stated, "Old mother is still alive. So, I thought I couldn't go away first". (ID: E)

Unfulfilled wishes

After the cancer diagnosis, some participants requested a second opinion. They hoped to somehow receive effective treatment and survive cancer. However, those doctors expressed harsh opinions, such as "It is too late to treat". The participants were disappointed because they felt that people with medical conditions like theirs might not be allowed to express that they want to live: "At the time of the announcement, the doctor told me that the survival rate of pancreatic cancer was about five years even for Stage I people. I was in Stage IV, so I thought it would be impossible to survive". (ID: H)

"Maybe I can live"

A doctor at a research facility specializing in the treatment of advanced hepatobiliary-pancreatic cancer stated that participants were relieved when doctors presented a new regimen or announced that treatment would begin immediately. For instance, one of the participants stated the doctor denied the use of the term "terminal cancer". "The doctor said, ‘Who said? I only use the term terminal cancer when there is not one thing I can do'. I was very happy, because he said, ‘Let's do our best because there is still something I can do'." (ID: E)

Continuing treatment and living as long as possible

Participants recognized that the only way to stay alive was to receive treatment. Those who experienced side effects such as peripheral neuropathy were concerned that worsening of symptoms would prevent their visit to the hospital; hence, their desire for receiving an effective drug was stronger than their fear of treatment. One of them reported, "I'm just hoping that this treatment will go well now. I have the goal of staying alive for as long as possible". (ID: C)

Want to continue planning the future even with illness

Participants said they were jealous of the elderly after being notified of the cancer because they could not imagine themselves living for 10 more years and thought they had no choice but to suffer from intractable

cancer. These participants were unambitious and set realistic goals to remain calm in the days ahead. One of them stated, "I have a daughter in the third year of college. I wish I could see her as a bride and the face of a grandchild. I used to think that I would live long until I was 80 years old, but now I wish I could live for 5 years... 10 years". (ID: F)

Constantly anticipating death

Despite feeling hopeful during the treatment, participants always felt profound anxiety. One of them reported feeling a lack of time and, in urgency, told their family to prepare for death. However, there were instances where participants reported avoiding discussions with family and friends about cancer-related anxiety and dying due to the seriousness and privacy of the matter. In fact, one participant stated, "I don't want to be distracted by telling my friends so many negative things, so I won't tell them. You have to be prepared... But... I'm worried about the death in front of me... Even though I am prepared...". (ID: I)

Willingness to do anything to stay alive

Participants did their best to survive during treatment. They remained self-motivated by believing that there might be a cure one day. Consequently, they collected a wide range of information on advanced and alternative medicine on the Internet. Some even expressed their willingness to participate in new clinical trials. In fact, one of them reported, "I'd like to talk to my doctor about combining treatments that are not covered by insurance. I don't have the evidence. It depends on how your doctor decides...". (ID: O)

Death may be difficult to overcome this time

When the therapeutic effect of the treatment started to wear off, one of the participants lost physical strength and motivation to fight due to weakness and difficulty in commuting. In addition, those who hoped to survive through the third line of treatment were disappointed when their doctor recommended hospice care rather than the third line of treatment. One of them reported, "When I went to visit a hospice, the doctor there told me, 'I think hospice is better than living on third rate drugs'... At this point, it seems that treatment or no treatment will make no difference". (ID: B)

Do not want to die

When an undulation of the therapeutic effect appeared, participants became increasingly motivated to continue their current treatment and extend their lives. However, one of the patients refrained from communicating with family and medical staff to avoid confusion or sadness. Talking to a medical practitioner about home care and hospice distressed another patient, as this gave the impression of accepting death. The patient stated, "We asked Mr. A from the Cancer Counseling Support Office to introduce us to the people at the Regional Comprehensive Center. I decided to ask about home-visit nursing. But I don't really want to die... I want to live a little longer for my son and my husband". (ID: H)

Structural diagram of desire to live in patients with advanced hepatobiliary-pancreatic cancer for whom curative treatment is not indicated

Figure 1 is a structured representation of the changes in desire to live during the five phases. In investigating the characteristics of each category, "positivity toward life" was shown as a white ellipse, "negativity toward life" was shaded, and "related to death" was black.

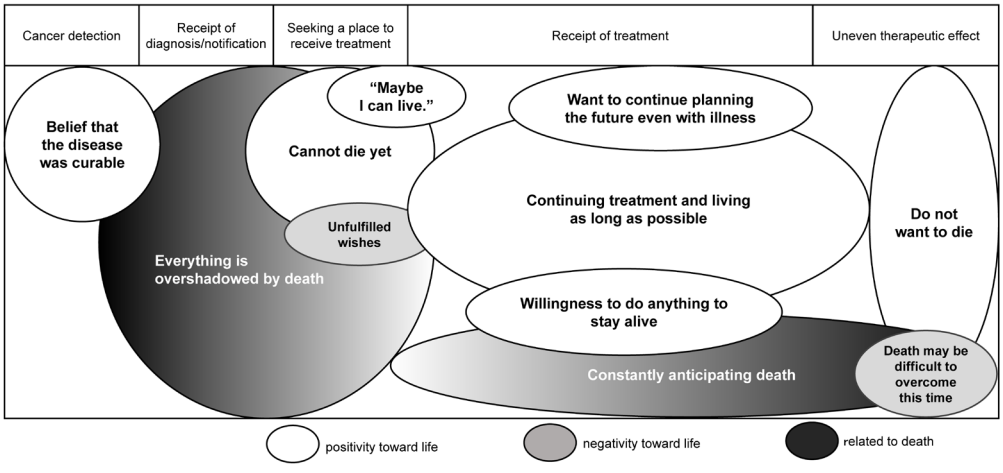

Figure 1. Structural diagram of desire to live in patients with advanced hepatobiliary-pancreatic cancer for whom curative treatment is not indicated. The medical treatment process experienced by patients with advanced hepatobiliary pancreatic cancer who are not indicated for curative treatment is shown in five stages, and the category of desire to live is placed there. Patients continued to express their desire to live in various ways, such as positive or negative, and using the word death.

An overview of Figure 1 shows that patients experienced changes in their desire to live and have an uninterrupted involvement in all the phases of treatment. Their expressions were diverse and associated with life-threatening events. Patients revealed feeling positive as well as negative toward dying, even though the treatment made them hopeful. The illustration of the desire to live provides an overview of the extracted categories and the observations of patients trying to stay alive.

Discussion

Aspects of patients with advanced hepatobiliary-pancreatic cancer for whom curative treatment is not indicated

This study assessed the desire to live, based on the events they experienced during the treatment and recuperation process, in patients with advanced hepatobiliary-pancreatic cancer who had been excluded from curative treatment. By dividing their experience into five phases and structuring the categories, it became clear that the patients' desire to live undergoes changes depending on their situations and that multiple thoughts can occur in conflicting times. These patients were found to have an uninterrupted – sometimes complex – expression of the desire to live. The desire to live in patients with advanced hepatobiliary-pancreatic cancer who had been excluded from curative treatment began with their belief that their disease was curable. However, after the diagnosis of refractory cancer and receiving a series of discouraging news, their feelings of positivity toward life diminished and they surrendered to death. Nevertheless, some participants insisted that they could not die yet because of their loved ones and fought to live through self-help. In the likelihood of being unable to regain their will to live, they might have abandoned the opportunity to survive, resulting in abandonment of information gathering and treatment. It is important to help patients with intractable or difficult-to-cure cancers find a place to receive treatment as soon as possible.

During the treatment period, the participants remained positive, yet also realistic and unassuming, while thoughts of death existed in them. The words and actions of patients with advanced cancer anticipating death have various meanings, including "an expression of the will to live" and "a desperate cry describing the misery of the present" (*28*). The narratives of death by patients who have incurable cancer should not be isolated from their desire to live. We need to be mindful of the fact that patients' narratives may paradoxically express a desire to live. In addition, the fact that there are many ways of expressing the desire to live suggests that patients are in control of their desire to live. The participants in this study were aware that their disease was incurable and the future was uncertain; thus, they did not have a strong desire to live. The more advanced the cancer is, the greater the focus of healthcare professionals may be on the treatment, and the lesser they may be able to recognize a patient's desire to live. Therefore, it is important for medical professionals to understand that such patients continue to desire living and offer an environment in which they can express it.

The results of this study verbalize the sensitive and sincere feelings of patients and will be an important resource for understanding not only advanced hepatobiliary-pancreatic cancer but also intractable cancer in Stage IV patients. We believe that this study will contribute to nursing support for patients with intractable and advanced cancers.

The importance of patients expressing their desire to live

This study found that patients were careful not to bring up serious topics in conversation with family and friends during treatment. It is also possible that they did not consult any medical professional during their treatment, nor did they think of doing so. Perception of refractory and Stage IV cancer may be one of the reasons for participants being unable to express their feelings to others. In Japanese media and on the Internet, there is an increasing amount of negative published content about intractable cancers such as advanced hepatobiliary-pancreatic cancer. Furthermore, some healthcare providers have classified patients with Stage IV intractable cancers as being near the terminal stage, that is, as "dying people". Such prejudice makes patients even more distressed (*15*). The more negatively people and healthcare providers perceive the course of a patient's life as incurable, the more difficult it will be for the patient to express that he or she wants to live.

Fortunately, with the accelerating development of new drugs, the number of patients with Stage IV refractory cancer who can maintain their health by continuing treatment is increasing. The survival rates for liver and pancreatic cancer in Japan are generally improving (*1*). The development of advanced medicine, new treatments, and measures to reduce side effects will enable patients with intractable cancers to extend their lifespan. Thus, it is necessary for medical practitioners to change the existing value system with the progress in medicine and medical care and dispel their perception of Stage IV intractable cancer.

Recently, the importance of Narrative Based Medicine in considering patient-centered medicine has been increasing (*29,30*). However, it is not easy to draw a story from the patients who keep their thoughts to themselves. Nurses can largely contribute to deciphering the messages behind the patients' words and work to understand the patients' desire to live. Furthermore, the ability to carefully interpret the patients' symptoms and feelings and to read their silence is also essential. Creating a medical treatment environment in which

patients can express their desire to live will not only help patients to process complicated information but also come to terms and have a better understanding of their suppressed feelings. A previous study reported that sometimes, speaking can create healing effects for patients themselves (*31*). When patients communicate their desire to live, healthcare providers need to be receptive and exercise patient-centered medical care. Ultimately, even if the treatment is interrupted, healthcare providers should consider the patients' desire to live as realistic and willingly seek ways to empathize with the patients.

Limitations

In this study, theoretical sampling was performed at medical institutions that specialize in the treatment of hepatobiliary-pancreatic cancer. Although there were patients from all over the country, the number of cancer types was biased due to the scarcity of patients with biliary tract cancer and the exclusion of several candidates for liver cancer.

In future studies, it would be useful to expand the number of facilities to verify the results of this study and examine specific nursing support measures that reinforce patients' desire to live.

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Parental detention and psychosocial wellbeing of migrant children in Japan

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Abstract: Immigration policies in Japan and elsewhere have been toughened in recent years. To investigate the potential effects of parental detention on migrant children, psychosocial wellbeing of children from migrant families with and without parental detention was compared. In this cross-sectional study, adult asylum seekers and migrant workers with children staying in Japan were invited through non-governmental organizations to answer a self-administered anonymous questionnaire in June and July 2020. Children's psychosocial wellbeing was assessed based on the Strength and Difficulties Questionnaire. In the 49 participating families, including 28 where either parent had ever been detained in Japan, there were 85 children aged 4-17 years who were subject to the analyses. Psychosocial wellbeing of children in families with parental detention appeared to be worse than that of their counterparts, especially on the dimension of emotional problems. More attention should be paid to the wellbeing of migrant children in Japan's immigration policy.

***Keywords*:** imprisonment, mental health, human migration, vulnerable populations

Introduction

Globally, the migrant population is growing substantially. In the past 20 years, the number of international migrants, refugees, and internally displaced persons increased from 150 to 272 million, from 14 to 26 million, and from 21 to 41 million, respectively (*1*). Even in Japan, there has been a large increase in the migrant population. In the past 10 years, the number of migrant workers and asylum seekers has increased about three-fold and nine-fold, respectively, with over 1.6 million migrant workers and over 10,000 asylum seekers in 2019 (*2,3*). In the same year, the number of unauthorized foreign nationals including migrant workers and asylum seekers was estimated to be nearly 80,000 (*4*).

In Japan, unauthorized foreign nationals are subject to detention and deportation. During the deportation process, they might be detained in immigration centers for an indeterminate period, even if they are seeking asylum or accompanied by children. Consequently, in violation of one of the rights endorsed in the United Nations Convention on the Rights of the Child, children are separated from their parents against their will (*5*).

With the increase in detention duration owing to stringent immigration policies in recent years, concerns have been raised about the harmful effects of parental detention on children's wellbeing (*6*). While the psychosocial impact of immigration policies has been well documented in the United States (*7,8*), this issue should be further highlighted for the sake of child protection in countries with stricter immigration policies. The present study, therefore, investigated the potential association of parental detention with psychosocial wellbeing of migrant children, including those seeking asylum in Japan.

Participants, Data collection, Measure, and Analysis

i) *Participants*. The participants were adult asylum seekers and migrant workers staying in Japan. The inclusion criteria were those accompanied by at least one child aged 4-17 and those who were literate, owing to the use of a self-administered questionnaire. They were recruited through non-governmental organizations supporting asylum seekers and migrant workers. This study was approved by the Research Ethics Committee of the Faculty of Medicine at the University of Tsukuba (No. 1505).

ii) *Data collection*. A self-administered anonymous questionnaire in the language the participants understand was sent to and collected from them through the non-governmental organizations. Since there was no definitive list of participants, approximately 100 individuals were invited, and 49 eligible participants answered the questionnaire in June and July 2020.

iii) *Measures*. Children's psychosocial wellbeing was assessed with the Strength and Difficulties Questionnaire (SDQ) (*9*). The SDQ consists of 25 items, with five

each across five subscales (emotional problems, conduct disorders, hyperactivity, peer problems, and prosocial behavior) rated on a three-point scale from 0 (not true) to 2 (certainly true) by the parents or teachers of the children. Each subscale score ranges from 0 to 10. The sum of four subscale scores excluding prosocial behavior provides a "total difficulties" score ranging from 0 to 40. The SDQ has been translated, validated, and made available in more than 80 languages (*https://sdqinfo.org/*).

The characteristics of the participants and their families included age, sex, country of origin, marital status, length of stay in Japan, cohabitants, engagement in a paid job, refugee application, detention experience in Japan, perceived social capital and support in Japan, and children's age, sex, and schooling. Perceived social capital and support were assessed based on a total of four questions (*10,11*). Social capital was assessed through two questions concerning social trust and mutual aid rated on a five-point scale, with responses of "yes" and "somewhat" categorized as "yes". Social support was assessed through two yes/no questions concerning emotional and instrumental support. The questionnaire will be made available upon request to the author.

iv) *Analysis*. First, the characteristics of participants and families with and without parental detention in Japan were described. Then, children's psychosocial wellbeing scores were compared between families with and without parental detention to examine the potential association of parental detention with children's wellbeing. Mean scale score differences and 95% confidence intervals between the two groups of children were estimated in multilevel regression analyses controlling for the covariates of child's age and sex at the individual level and the family at the group level. Multilevel analyses were used to consider a clustered structure of the data (*i.e.*, children within the family).

Key findings and discussion

There were 49 participants/families that met the inclusion criteria. Participants' mean age was 42 years, 29 (59%) were males, 37 (76%) came from Asian countries, 45 (92%) were married, 35 (71%) had spent 10 years or longer in Japan, and the median number of cohabitants was four. Of the 49 families, 28 (57%) had at least one parent engaged in a paid job in Japan, 30 (61%) had at least one parent in the process of refugee application, 28 (57%) had at least one parent who had ever been detained in Japan, and 13 of 28 reported that the length of detention was one year or longer. Regarding the participants' perception of social capital and support, 14 (29%) and 15 (31%) perceived social trust and mutual aid in the community, respectively, and 32 (65%) and 31 (63%) perceived emotional and instrumental support in their social network, respectively. In the 49 families, there were 85 children aged 4-17 years subject to the subsequent analyses. Their mean age was nine years, and 37 (44%) were males. All school-aged children were in school.

Table 1 compares the characteristics mentioned above between the families with and without parental detention, showing discernable differences by length of stay in Japan and refugee application. Families with parental detention had spent a longer time in Japan and had more refugee applications than their counterparts. Table 2 shows the mean scale score of psychosocial wellbeing among children in families with and without parental detention, and the estimated mean differences between these two groups. Children in families with parental detention had significantly higher scores, especially on the subscale of emotional problems, than their counterparts, while there was no significant difference on the subscale of prosocial behavior.

Psychosocial wellbeing of children in families with parental detention appeared to be worse than that of their counterparts among asylum seekers and migrant workers in Japan. This finding is consistent with previous studies (*7,8*). So, it is plausible that parental detention would potentially harm children's wellbeing

Table 1. Characteristics of participants and their households by parental detention in Japan[a]

Variables	Ever detained	Never detained
Participants	(*n* = 28)	(*n* = 21)
Age, mean (SD)	42.4 (5.7)	40.4 (5.9)
Sex (male)	20	9
Geographic region of origin		
Asia	23	14
Africa	4	5
Others	1	2
Marital status		
Married	27	18
Single	0	3
Missing	1	
Length of stay in Japan (years)		
< 10	2	11
10-19	20	7
≥ 20	6	2
Missing		1
Number of cohabitants, median (IQR)	4 (3, 5)	3 (3, 5)
Paid job (yes)[b]	12	16
Refugee application (yes)[c]	25	5
Missing		4
Perceived social capital		
Social trust (yes)	8	6
Mutual aid (yes)	8	7
Perceived social support		
Emotional support (yes)	17	15
Instrumental support (yes)	19	12
Children aged 4 to 17 years	(*n* = 49)	(*n* = 36)
Age, mean (SD)	9.1 (3.9)	8.8 (3.4)
Sex (male)	24	13
Missing	1	1

SD: standard deviation, IQR: interquartile range. [a]Households were classified as "ever detained" if either parent had ever been detained in Japan. [b]Yes if either parent had a paid job. [c]Yes if either parent was applying for refugee status.

Table 2. Mean scores of children's psychosocial wellbeing[a] by parental detention, and mean difference estimated in multilevel regression analyses[b]

Variables	Ever detained Mean	Never detained Mean	Mean difference (95% CI)
Emotional problems	4.59	1.72	2.38 (0.68, 4.07)
Conduct disorders	3.00	1.44	1.36 (0.26, 2.48)
Hyperactivity	4.35	3.03	1.14 (0.31, 1.97)
Peer problems	3.27	2.31	0.85 (0.06, 1.65)
Prosocial behavior	7.31	8.14	-0.74 (-1.94, 0.46)
Total difficulties[c]	15.20	8.50	5.46 (1.55, 9.38)

CI: confidence interval. [a]Measured using the Strength and Difficulties Questionnaire. [b]Controlling for child's age and sex at the individual level and household at the group level. The analyses excluded two children whose sex was not reported. [c]Total difficulties score is the sum of subscale scores excluding prosocial behavior.

in migrant populations in Japan, posing an unescapable question: is it still justifiable to let innocent children sacrifice their fundamental right to be with their parents? Japan's immigration policy should be considerate to the wellbeing of migrant children.

This study had several limitations. First, it is difficult to make causal inferences regarding the relationship between parental detention and children's wellbeing because changes in wellbeing before, during, and after parental detention were not examined; instead, the study involved a cross-sectional comparison of the wellbeing of children in families with and without parental detention. Yet, this does not entirely negate the potential effect of parental detention on children's wellbeing, given that parental detention was independent of children's wellbeing. Therefore, the wellbeing of children in families with and without parental detention could have been comparable before parental detention, unless children in families with parental detention tended to have any predisposing factors affecting their wellbeing. If wellbeing was comparable before parental detention, differences in the wellbeing of children in the two types of families might have been due, at least in part, to parental detention.

Second, children's psychosocial wellbeing was assessed by their parents. While this is the standard assessment method for the SDQ, one might assume that the evaluation of children's wellbeing was influenced by the wellbeing of the parents, and the magnitude of this influence was greater for those who had ever been detained than those who had never been detained; consequently, children's wellbeing scores were inflated in the former. However, the subscale scores rated by those who had ever been detained were not evenly greater than the scores rated by those never detained. This might imply that even if the subscale scores were somewhat inflated, they still reflected the potential effects of parental detention.

Third, the sample size was too small to analyze the relationship between length of parental detention and children's wellbeing. Moreover, as there were no families where a parent was in detention during the study period, the impact of current detention could not be examined. Such analyses will help establish causality. Finally, the participants were recruited through non-governmental organizations, so those not accessible were not included in this study. It is uncertain whether they were better off, not requiring any support, or hidden for legal reasons. Besides, about half of those contacted did not reply. It is also uncertain whether their characteristics were different from the participants'. In any case, the findings have important implications for immigration policy in light of child protection.

In conclusion, psychosocial wellbeing of children in families with parental detention was worse than that of their counterparts among asylum seekers and migrant workers in Japan. More attention should be paid to the wellbeing of migrant children in Japan's immigration policy.

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The advances in dealing with the safety of medicated drugs in pregnancy

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Abstract: The Japan Drug Information Institute in Pregnancy (JDIIP) was established with the aims of providing information on drug safety to women who are worried about drug use during pregnancy and creating evidence through epidemiological studies based on counseling cases. Since being established, JDIIP has made many contributions to the wellness of mothers and children by promoting the proper use of drugs during pregnancy. A network consisting of Core hospitals in 47 prefectures plays an important role in providing information for women living anywhere in Japan. Because cases of exposure to drugs whose safety we want to analyze are usually rare, networks of domestic and foreign teratology information services are necessary in order to produce high-quality evidence. JDIIP has been contributing to the education of pharmacists and doctors and to the creation of clinical practice guidelines in various medical societies by using keywords such as "pregnancy" and "medication". Future issues include creating an environment that is easily accessible for those seeking consultation, building a mechanism that makes it easy to create a basis for safety, and aiming for the continuing development of the organization.

***Keywords*:** drug safety, pregnancy, counseling, epidemiological study

Introduction

The thalidomide tragedy led to persistent concerns that using drugs during pregnancy causes fetal congenital anomalies. This has led to negative behaviors in women who are undergoing drug therapy for existing conditions, such as avoiding becoming pregnant or discontinuing necessary medications during pregnancy. There have been incidents of abortion among women who used drugs without realizing they were pregnant. Skilled counseling based on evidence is needed to relieve these anxieties. However, there were few skilled counselors and little quality evidence required for counseling in this field. The only safety-related evidence available when new drugs are launched is derived from animal studies. However, the results of these studies are not necessarily applicable to humans. Evaluation of risks during pregnancy should in principle be based on epidemiological research.

It became clear that counseling and epidemiological research systems were needed. To address these problems, the Japan Drug Information Institute in Pregnancy (JDIIP) was founded as a teratology information service (TIS) by the Ministry of Health, Labour and Welfare (MHLW) in 2005 at the National Center for Child Health and Development (NCCHD). Prior to opening, we received guidance from both Toranomon Hospital which had already started a Counseling Clinic for "Pregnancy and Medicine" in 1988, and also The MotheRisk Program (MRP) which was established at the Hospital for Sick Children (Toronto, Canada) in 1985 (*1*).

Besides MRP, several TIS were also established in Europe and North America. The European Network of Teratology Information Services (ENTIS) is made up of 17 TIS locations in Europe, starting with TIS, which was opened in 1990 in Milan, and 5 other TIS located in Asia and South America including JDIIP (*2*). The Organization of Teratology Information Specialists (OTIS), founded in the United States in 1999, consists of many members, including JDIIP members, and has published many papers through multicenter research. In 2013, OTIS announced MotherToBaby, a name for its public-facing service and research studies (*3*).

The Nordic countries have generated high-quality evidence of drug safety during pregnancy using personal identity number systems and midwifery interview systems (*4*).

Services provided by JDIIP (What does it do?)

The three main services provided by JDIIP are counseling regarding the safety of drug use during pregnancy, establishing evidence regarding the safety of drug use during pregnancy based on counseling cases, and recommending revisions of drug package inserts based on risk-benefit considerations in pregnant or nursing women. The medical staff of JDIIP consists of pharmacists and physicians, the latter of whom specialize in obstetrics, internal medicine, or neonatology (pediatrics). In addition, specialists in congenital anomalies are involved as consultants.

Counseling

JDIIP provides consultations for women who are concerned about the safety of drug use during pregnancy. At a meeting of experts prior to the foundation of JDIIP, face-to-face counseling was instructed for women taking high-risk drugs. Accordingly, core hospitals were designated in 47 prefectures nationwide, including the NCCHD Hospital, and consultation is now provided by "outpatient clinics for pregnancy and drugs" at these core hospitals (Figure 1).

In principle, we provide counseling based on epidemiological data by weighing risks and benefits. The original JDIIP safety information that is used in counseling is referred to as the "JDIIP-Summary". It was prepared by scrutinizing and summarizing information from a source often referred to as "Briggs" (*5*), a book compiling epidemiological studies on the safety of drugs during pregnancy, as well as databases of third-order information including Reprotox (*6*), the Teratogen Information System (TERIS) (*7*), and MRP (*1*) (Figure 2). The disadvantage of these third-order databases is that the data are not updated on a real-time basis. Therefore, in every consultation, JDIIP checks Medline or the information published by pharmaceutical companies and adds necessary information, if any. For drugs developed in Japan that are not available in English-speaking countries, there are almost no epidemiological data regarding their use during pregnancy. In such cases, JDIIP searches Japan Medical Abstracts or retrieves Interview Forms and makes inquiries to pharmaceutical companies if necessary (Figure 2). In order to ensure that the information JDIIP provides is correct, meetings of the JDIIP-Summary Review Committee, which includes external members, are regularly hosted by the department in charge at the MHLW.

There are three consultation methods: *i*) counseling at the "outpatient clinics for pregnancy and drugs" at the core hospitals mentioned above, *ii*) explanations provided by physicians who are treating clients based on the safety information sent from the office, and *iii*) counseling over the phone by medical staff members of JDIIP. Upon receiving the questionnaire, the office arranges a consultation method based on the preference of the client and the characteristics of the drugs concerned. From October 2005, when JDIIP was founded, to November 30, 2020, there were 15,601 consultations (6,276 before conception and 9,455 during pregnancy) regarding the use of drugs during pregnancy, and 7,434 consultations regarding the use of drugs during breastfeeding. We demonstrated that the counseling provided by JDIIP is effective because it reduces the anxiety in women

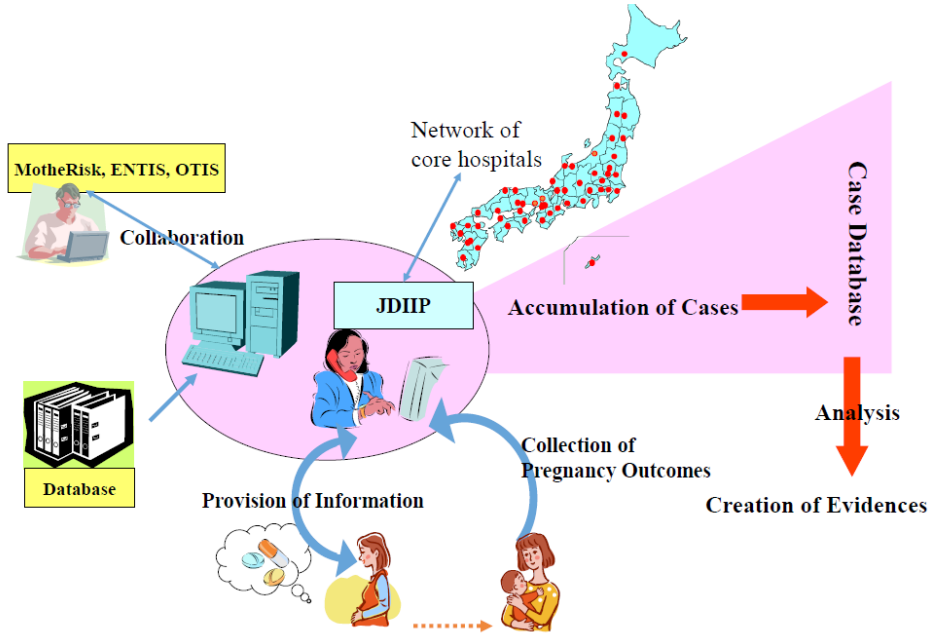

Figure 1. Japan Drug Information Institute in Pregnancy (JDIIP). The main tasks of JDIIP are counseling and establishing evidence regarding the safety of drug use during pregnancy. The core hospitals were designated in 47 prefectures nationwide and consultation is provided by "outpatient clinics for pregnancy and drugs" at these core hospitals.

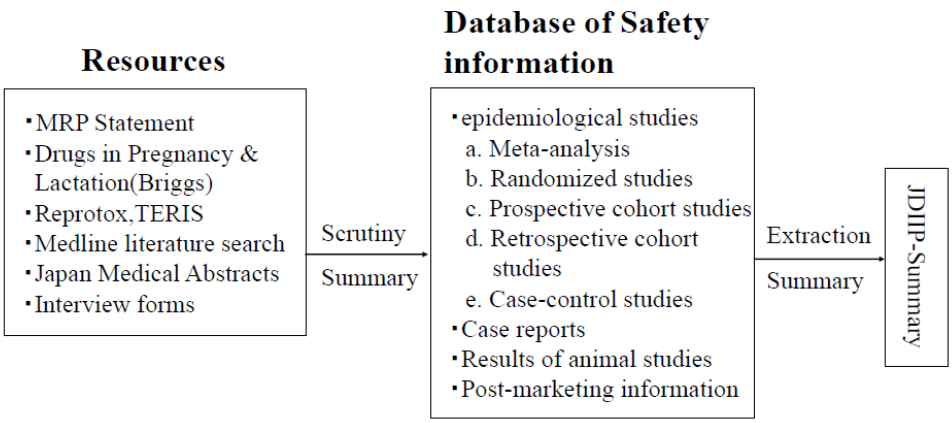

Figure 2. Method for preparation of information to be provided. The original JDIIP safety information that is used in counseling is referred to as the "JDIIP-Summary". It was prepared by scrutinizing and summarizing the information from third-order databases such as "Briggs" (*3*), Reprotox (*4*), TERIS (*5*), and MRP (*6*). Furthermore, in every consultation, Medline or the information published by pharmaceutical companies are checked.

who are using drugs during pregnancy. This resulted in increased deliveries for women, who would otherwise hesitate to continue pregnancy due to excessive concern about drug risks (*8*).

Generation of evidence

The medical questionnaire completed by clients includes columns for the names of relevant drugs, their doses, and their indications. Consultees are also asked to provide their age, height, body weight, history of folic acid intake, and history of pregnancy, as all of these can be confounding factors regarding safety. For consultations during pregnancy, JDIIP sends clients a survey card 1 month after the expected delivery date asking them to provide the results of pregnancy and the presence or absence of congenital abnormalities. Based on this approach, JDIIP requested that 9,455 pregnant women who consulted JDIIP from October 2005 to November 30, 2020, participate in a survey of pregnancy results; 8,378 women provided consent, and 6,816 returned their survey cards. The response rate was 81.4%, which is considered to be relatively high among studies in this field. In this way, JDIIP established a methodology for safety analysis based on information regarding drug use and pregnancy results, *i.e.*, for prospective cohort research starting from the time of consultation.

Using this methodology, JDIIP has analyzed several drugs and presented or published the results at academic meetings or in journals (*9,10*). In particular, the authors were the first worldwide to report on the safety of oseltamivir (*11*) during the outbreak of a new type of influenza. In order to assess if risks are unlikely, more than 300 cases exposed to a target drug are needed. For several years, JDIIP has been working on publishing evidence regarding drug safety during pregnancy with the combined data of JDIIP and Toranomon Hospital using public funding. It is hoped that this plan will show the safety of drugs developed in Japan for which evidence has thus far been scarce (*12*).

Recommendation regarding revision of package inserts

For almost all drugs that are contraindicated in pregnant women based on animal studies, the contraindication is not reversed even after the risk during pregnancy is ruled out based on epidemiological studies. That is to say, the use of these drugs continues to be avoided in the treatment of pregnant women who need them. Practice guidelines can solve this problem. While package inserts are prepared by pharmaceutical companies, practice guidelines are developed mainly by physicians. Confusion tends to occur in medical practice regarding which should be followed when there are discrepancies between them. To address this issue, MHLW started a project to promote the proper use of drugs in pregnant or nursing women in 2016. JDIIP is responsible for examining the data from animal studies and epidemiological research as well as those regarding clinical utility in cooperation with external experts, and submitting the results to the MHLW. As the first accomplishment of this project, the phrase "contraindicated during pregnancy" in the package inserts of immunosuppressants such as tacrolimus, cyclosporine, and azathioprine, was successfully changed to "can be used during pregnancy if needed" in 2018. Similar efforts are currently being made for calcium blockers.

Education and social responsibility (How does JDIIP contribute to society?)

Once a year, JDIIP offers seminars for physicians and pharmacists at core hospitals and organizes a public symposium on a timely theme. In addition, JDIIP provides educational lectures in response to invitations by academic associations, medical associations, and

pharmacist associations. Moreover, members of JDIIP have published multiple textbooks in this field. JDIIP is also involved in the development of practice guidelines at the request of academic associations, such as the Japanese Society of Nephrology, the Japanese Circulation Society, the Japan Society for Adult Congenital Heart Disease, the Japanese Society of Hypertension, the Japan College of Rheumatology, the Japanese Dermatological Association, and the Japan Society for Transplantation.

Future vision (What is JDIIP going to do?)

Counseling

The results of the Japan Environment and Children's Study indicate that 70% of pregnant women use drugs, including supplements (*13*). Moreover, the numbers of consultations over the phone and at outpatient clinics handled by the Teratology Information Service (TIS) of Korea, were 10,721 and 253 respectively in 2015 (personal communication). JDIIP is clearly far from fulfilling the needs of the Japanese population. It is suspected that the counseling service is not sufficiently utilized by the women who need it. To make the process even easier for users, the pre-counseling procedures should be simplified. Currently, JDIIP is considering an IT-based method for accessing the service. JDIIP is also planning to collaborate with pharmacists at core hospitals nationwide and at local pharmacies to increase awareness of methods for using the services offered by JDIIP (mainly through core hospitals) and to disseminate knowledge in this field.

Generation of evidence

Discussions regarding the use of drugs for chronic diseases during pregnancy are often held between patients and their physicians and do not frequently lead to consultations with JDIIP. Therefore, JDIIP needs to proactively include these drugs in its databases. Currently, several epidemiological research projects that use JDIIP as a platform for registry systems are underway. JDIIP and core hospitals will conduct registry surveys of certain drugs in collaboration with academic associations and research groups. JDIIP will also explore the coordination of its services with post-marketing surveillance by pharmaceutical companies.

International collaborative research is essential for achievement of high quality results in epidemiological studies, particularly in this area where it is difficult to gather information on existing cases. JDIIP has had contact with MRP, ENTIS, and OTIS, and recently started conducting joint research with them.

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The profile of patients hospitalized with COVID-19 under the Quarantine Act in a designated hospital near an international airport in Japan

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Abstract: The Japanese Government has implemented quarantine measures in response to the COVID-19 pandemic. Individuals testing positive at the airport's quarantine office were lodged either in a designated hotel or hospital under the Quarantine Act. The aim of this study is to describe the management of patients with COVID-19 admitted under the Quarantine Act and to evaluate its impact on medical resources. Data were retrospectively collected, including demographics, comorbidities, status at admission, clinical condition, treatment, outcomes, status at discharge, duration of hospitalization, and the cost of hospitalization for all patients hospitalized with COVID-19 at this facility under the Quarantine Act between January 2020 and April 2021. A total of 48 patients (39 males, 9 females; median age: 38.5 years) with COVID-19, half (52.1%) of which were Japanese, were hospitalized under the Quarantine Act. The majority (87.5%) of the patients lived or planned to stay outside of Chiba Prefecture. The most frequent time of admission was 9 PM–1 AM. Hypoxia on admission was observed in 10 (20.8%) patients and oxygen therapy was provided to 8 (16.7%). One patient died due to respiratory failure. The median duration of hospitalization was 11 days. The total cost of hospitalization was 82,705,289 yen (approximately $760,000), which was covered by public funds. Patients hospitalized with COVID-19 under the Quarantine Act were younger and less severely ill than inpatients with COVID-19 from among the general population in Japan (according to a COVID-19 registry), but consumed a significant amount of medical resources at this hospital. An efficient system to manage patients with COVID-19 in designated hotels should be created and indications for hospitalization should be determined.

***Keywords*:** COVID-19, quarantine office, international airport, Chiba Prefecture

The Japanese Government has implemented quarantine measures in response to the COVID-19 pandemic. After COVID-19 was designated a quarantinable infectious disease in Japan on January 28, 2020 (*1*), quarantine officers started testing international travelers for symptomatic and suspected cases of COVID-19. On March 9, 2020, entry restrictions were tightened, and quarantine measures were strengthened to include testing of asymptomatic travelers and isolation for travelers who test positive (*2*).

As of May 1, 2021, all international travelers must submit a certificate of negative test result of pre-entry COVID-19 test conducted within 72 hours prior to departing from the country/region where they were staying and undergo a quantitative antigen test or nucleic acid amplification test upon arrival. In addition, those who have stayed in countries/regions with community transmission of SARS-CoV-2 variants of concern in the previous 14 days are required to self-quarantine for 3 days at a location designated by the quarantine station chief and to take a test again on the third day. If the test is positive, quarantine is conducted in accordance with the Quarantine Act. Even if all test results are negative, self-quarantine at home or in a hotel is required until completing the remainder of the 14-day self-quarantine period (*3,4*). Initially, all patients testing positive were admitted to a designated hospital. At present, asymptomatic positive individuals and those with mild symptoms are quarantined in a designated hotel.

The Japan Ministry of Health, Labor, and Welfare has reported 2,687 cases (of the 641,842 tests performed) of COVID-19, including 116 patients who required inpatient treatment confirmed at the quarantine office prior to May 1, 2021 (*5*). However, the Ministry has not released detailed information about those patients. The current authors' hospital is one of the designated

hospitals caring for patients with COVID-19 sent by the local government under the Infectious Diseases Control Act as well as patients with COVID-19 sent by quarantine offices under the Quarantine Act. Admitting patients under the Quarantine Act in the middle of a local epidemic is a heavy burden and can affect the local healthcare system.

The purpose of this study is to describe the profile of patients with COVID-19 admitted to this hospital and to evaluate the impact of admitting patients referred from the quarantine office under the Quarantine Act.

This hospital-based, retrospective cohort study was conducted at the Japanese Red Cross Narita Hospital, a large tertiary teaching hospital with 716 beds, located 20-minutes' drive from Narita International Airport in Chiba, Japan. This hospital is one of the two major hospitals that treat patients from the Narita Airport Quarantine Station under the Quarantine Act. The study was approved by the Ethics Committee of the Japanese Red Cross Narita Hospital under the condition that the confidentiality of all personal data be maintained (JRCNH-718-01). Given the retrospective, observational nature of the study, the requirement for individual consent was waived.

Subjects included all patients with COVID-19 who were admitted under the Quarantine Act between January 2020 and April 2021. Information on these patients was obtained from this department's database. The diagnosis of COVID-19 was made based on either a nucleic acid amplification test or antigen quantification test. Patients with COVID-19 hospitalized under the Infectious Diseases Control Act were excluded.

Information on demographics, comorbidities, status at admission, clinical condition, treatment, outcome, status at discharge, and duration of hospitalization was retrospectively collected from electronic medical records. The cost of hospitalization was also ascertained for each patient. Categorical variables are shown as numbers and percentages and continuous variables are shown as medians and ranges.

In total, 48 patients were admitted to this hospital under the Quarantine Act during the study period. Table 1 summarizes the patients' demographics, characteristics, and comorbidities. The median patient age was 38.5 years, and 39 patients (81.3%) were males. Approximately half (52.1%) of the patients were Japanese. The most common comorbidity was diabetes (12.5%), followed by a chronic respiratory disease and obesity (6.3%). The region where the patient had been most frequently before arriving in Japan was South Asia (29.2%), followed by Southeast Asia (22.9%). The two primary reasons for international travel were business (43.8%) and visiting friends or relatives (39.6%). Most (87.5%) of the patients did not live in Chiba Prefecture or they had planned to stay outside of it.

Table 2 summarizes the patients' status at admission, treatments, outcomes, and costs. The reason for admission varied. One-third (35.4%) of the patients had either hypoxia or respiratory distress. Two patients were hospitalized for evaluation or treatment of other diseases, such as malaria or tuberculosis. Three other patients were hospitalized due to a language barrier, the need for a regularly prescribed medication, and uncontrolled diabetes. Two-thirds (64.6%) of the patients were transported to this hospital directly from the quarantine station at Narita International Airport, and the remaining patients (35.4%) were from the hotel designated by the quarantine office. The most frequent time of admission was 9 PM–1 AM. Hypoxia on admission was observed in 10 patients (20.8%) and oxygen therapy was provided for 8 (16.7%). Signs of pneumonia were found in 23 patients according to a chest X-ray and in 22 patients according to a computed tomography scan. Therapy with remdesivir was provided to 7 patients (14.6%). Steroids and anticoagulants were administered to 8 patients (16.7%). Most (89.6%) of the patients were discharged; 4 (8.3%) patients were transferred to a designated hotel because of the time needed to fulfill the discharge criteria. Only one patient died due to respiratory failure. The median duration of hospitalization was 11 days, and the total duration of hospitalization was 551 days.

Table 1. Patient demographics, characteristics, and comorbidities (n = 48)

Characteristics	Overall (n = 48)
Median age in years (range)	38.5 (0-74)
Sex: male/female	39/9 (81.3/18.8)
Ethnicity	
Japanese	25 (52.1)
Non-Japanese	23 (47.9)
Comorbidities*	
Diabetes	6 (12.5)
Chronic respiratory disease	3 (6.3)
Obesity	3 (6.3)
Cardiovascular disease	1 (2.1)
Cerebrovascular disease	0 (0)
Severe renal disease or dialysis	0 (0)
Solid tumor	0 (0)
Immunosuppression	0 (0)
Region the patient visited before arriving in Japan	
South Asia	14 (29.2)
Southeast Asia	11 (22.9)
North America	7 (14.6)
Africa	6 (12.5)
Europe	5 (10.4)
Central and South America	2 (4.2)
Central and West Asia	2 (4.2)
East Asia	1 (2.1)
Oceania	0 (0)
Purpose of international travel	
Business	21 (43.8)
Visiting friends or relatives	19 (39.6)
Study	4 (8.3)
Tourism	4 (8.3)
Place of residence or destination in Japan	
Chiba Prefecture	6 (12.5)
Other	42 (87.5)

*Each comorbidity is defined according to a previous study (*8*).

Table 2. Patients' status at admission, treatments, outcomes, and costs (n = 48)

Characteristics	Overall (n = 48)
Main reasons for admission	
Hypoxia/Respiratory distress	17 (35.4)
Other symptoms (*e.g.*, fever, cough, sore throat)	26 (54.2)
Evaluation or treatment of other diseases (pulmonary tuberculosis or an imported tropical disease)	2 (4.2)
Other (*e.g.*, language barrier, lack of regular medication, uncontrolled diabetes)	3 (6.3)
Location prior to hospitalization	
Airport*	31 (64.6)
Hotel designated by the quarantine office	17 (35.4)
Time of admission	
9 AM–1 PM	10 (20.8)
1 PM–5 PM	6 (12.5)
5 PM–9 PM	12 (25.0)
9 PM–1 AM	19 (39.6)
1 AM–5 AM	0 (0)
5 AM–9 AM	1 (2.1)
Hypoxia on admission	10 (20.8)
Signs of pneumonia on chest X-ray	23/39 (59.0)
Signs of pneumonia on CT scan	22/38 (57.9)
Supportive care	
Oxygen therapy	8 (16.7)
High-flow oxygen device	2 (4.2)
Medication	
Remdesivir	7 (14.6)
Favipiravir	1 (2.1)
Tocilizumab	1 (2.1)
Steroid	8 (16.7)
Anticoagulant	8 (16.7)
Outcomes	
Discharged home	43 (89.6)
Transferred to a designated hotel	4 (8.3)
Death	1 (2.1)
Median duration of hospitalization (range)	11 (3-25)
Total duration of hospitalization (days)	551
Total cost of hospitalization (Yen/US dollars)	82,705,289/757,652

*including one patient who was transported as a medical evacuee from Indonesia.

The total cost of hospitalization was 82,705,289 yen (approximately 760,000 US dollars), which was covered by public funds.

The current results indicated that patients hospitalized with COVID-19 under the Quarantine Act were younger and had less severe disease. In COVID-19 Registry Japan, the nationwide registry for COVID-19 in Japan (*6*), patients had a median age of 52 years, and 32.1% received oxygen therapy. In contrast, subjects of the current study had a median age of 38.5 years, and 16.7% received oxygen therapy. These differences were probably attributable to the fact that patients who are able to travel abroad are generally younger and healthier. One patient, who refused intubation and continued treatment with high-flow oxygen therapy, died. The rest of the patients recovered without sequalae.

Admitting mildly ill patients to the hospital under the Quarantine Act could negatively impact the hospital's capacity to receive local patients with COVID-19 during the pandemic. This hospital has allocated beds for patients with COVID-19 based on a contract with the Chiba Prefectural Government; admitting patients from the quarantine office will require the use of those beds. Given that 87.5% of the patients whose residence or destination in Japan was outside of Chiba Prefecture, the burden should not be limited solely to a few medical facilities near the airport. Many patients were transferred at night, which also consumed this hospital's medical resources.

The current results suggest that many of the patients transferred to this hospital could have stayed in a designated hotel with adequate medical support since the vast majority (83.3%) did not need oxygen therapy or medication for COVID-19. In addition, several patients had to be admitted for reasons unrelated to the disease, such as an inability to speak neither English nor Japanese. Several patients lacked regular medication and were thus transferred to this hospital. Since Fotheringham et al. reported that special health accommodations with the support of a virtual hospital contributed to an efficient quarantine process (*7*), remote medical management including telemedicine would help prevent unnecessary hospitalization and could save medical resources.

The current study had several limitations. First, it was a small-scale, single-center study and therefore does not reflect the characteristics of patients hospitalized with COVID-19 under the Quarantine Act throughout Japan. However, Narita Airport is the largest international airport in Japan and this hospital is one of two main hospitals admitting patients sent by the quarantine office at Narita Airport, so the current findings warrant consideration. In addition, the number of patients in this study represents one-third of the patients reported by the Government as requiring hospitalization under the Quarantine Act. Second, the criteria for admission and discharge under the Quarantine Act have changed over time, and the results could have been affected by changes in these criteria.

In conclusion, this retrospective cohort study has revealed that patients hospitalized with COVID-19 under the Quarantine Act were younger and less severely ill but consumed a significant amount of medical resources in the area near Narita Airport. An efficient system to manage patients in designated hotels should be created and indications for hospitalization should be determined using remote medical management, including telemedicine, in order to prevent unnecessary hospitalization and conserve medical resources in the local area.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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