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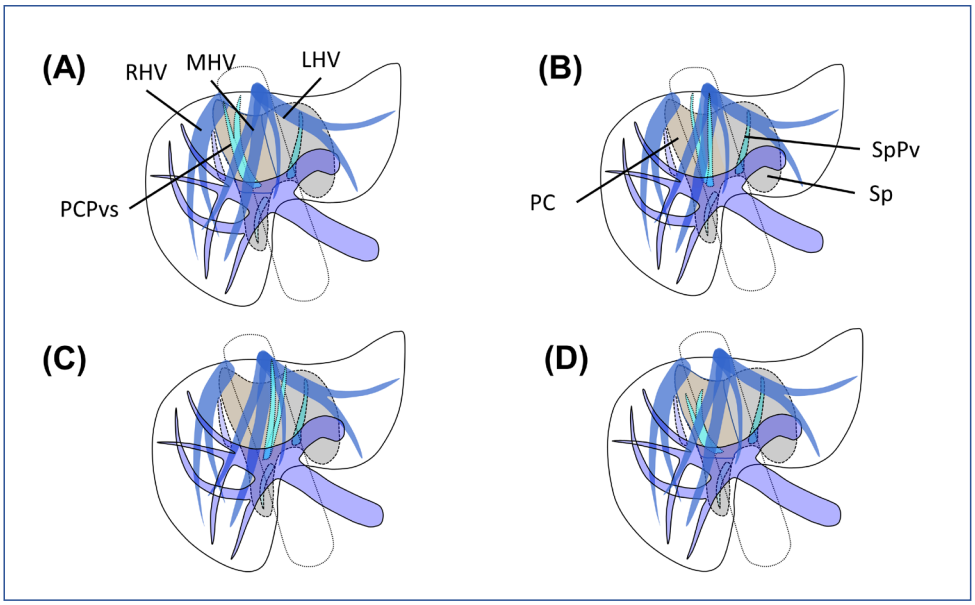

Four types of relationships between the paracaval portal vein branches (PCPVs) and the major hepatic veins (Pages 273-276)

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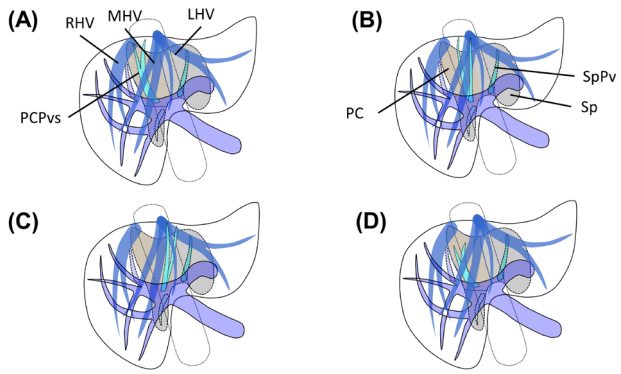

Four types of relationships between the PCPvs and the major hepatic veins. (A) Type RM, PCPvs reach the hepatic surface through the gap between the right and the middle hepatic veins (MHV); **(B)** Type M, PCPvs reached the hepatic surface through the branches of the MHV; **(C)** Type ML, PCPvs reached the hepatic surface through the gap between the MHV and left hepatic vein; **(D)** Type 0, PCPvs did not reach the hepatic surface. PCPvs, paracaval portal veins; RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; PC, paracaval portion; Sp, Spiegel lobe; SpPv, Spiegel portal vein. (Pages 273-276)

Global Health & Medicine. 2024; 6(4):225-235. ORIGINAL ARTICLE
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Employment status of older nursing staff aged 55 years and older in care facilities: A nationwide cross-sectional study in Japan

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Abstract: An aging nursing workforce requires addressing shortages due to retirement. This nationwide descriptive cross-sectional study in Japan clarified the employment status of older nursing staff aged ≥ 55 years by facility type during January–March 2022. Questionnaires were sent to 8,000 nursing directors, with 1,658 valid responses (response rate: 20.7%). Descriptive statistics and Kruskal–Wallis or χ^2 tests analyzed inter-facility differences. A violin plot depicted the proportion of older nursing staff across facilities by age group, and generalized estimating equation (GEE) models examined associated factors at the facility level. Older nursing staff's distribution differed significantly across age groups ($p < 0.01$), from 0% to 100% within the same facility type. Some facilities had high percentages of staff working beyond retirement age. GEE results showed higher percentages of full-time employees and nurses were negatively associated with the percentage of older nursing staff across most facility types ($p < 0.05$). For those aged ≥ 65 years, the total population was positively associated with employment in bedded clinics (coef. = 0.07, 95% CI: 0.01 to 0.14, $p = 0.03$), but negatively associated with the total population (coef. = -0.06, 95% CI: -0.10 to -0.01, $p = 0.02$) and percentage of the population aged ≥ 65 (coef. = -0.76, 95% CI: -1.43 to -0.08, $p = 0.03$) in long-term care insurance facilities. Working conditions and environments should be improvement to potentially retain older nursing staff. Job seekers should be matched with managers' needs in facilities with a higher proportion of older nursing staff to ensure a sustainable workforce.

***Keywords*:** aging, employment, nurse, retirement, workforce

Introduction

The aging nursing workforce poses significant challenges for many countries. According to the State of Global Nursing 2020, a report by the World Health Organization (*1*), one in six (*i.e.*, 17%) of the world's nurses are aged ≥ 55 years and are expected to retire within the next decade. Age-related retirement affects the entire nursing workforce and is a key global challenge (*2*). Consequently, retaining them in the workforce necessitates attention to individual and organizational factors, including attention to physical needs, flexible work arrangements, role redesign, development of educational programs, financial incentives, and respect for professional knowledge (*3-7*).

Japan, with the world's largest aging population, must lead in addressing this challenge (*8*). The number of nursing staff in Japan increased by 33.3% from 2007 to 2022. The proportion of employed nursing staff in their 40s slightly decreased from 25.8% in 2007 to 25.4% in 2022, while those in their 50s rose from 17.4% to 22.1%, and those aged ≥ 60 years increased from 4.5% to 12.9%. The proportion of older nursing staff aged ≥ 55 years also grew from 9.4% in 2007 to 23.0% in 2022, reflecting the aging trend in Japan's nursing workforce (*9*).

Japan's mandatory retirement age system, prevalent across industries, poses a concern for the nursing profession. Typically, labor contracts terminate when workers reach a predetermined age set by their organization, commonly 60 years for nurses (*10,11*). According to the 2017 General Survey on Working Conditions, 95.5% of industries have a mandatory retirement age, with 79.3% of them setting this age at 60 years (*12*). These findings are consistent with the results of a 2019 hospital survey, which also reported that the majority of hospitals set the retirement age for nurses at 60 years (*13*). There is growing apprehension regarding the potential mass retirement of nurses and their exit from the nursing labor market.

In several countries, including the United States, efforts to eliminate age discrimination, such as the Age Discrimination in Employment Act of 1967, which

raises the age at which pension benefits begin (*14*) and eliminates or raises the retirement age, seek to ensure the continued employment of older nurses (*15-17*). In 2004, the Japanese government enacted the "Law Concerning Stabilization of Employment of Older Persons" to alleviate restrictions on the employment of older individuals caused by the mandatory retirement age (*18*). Although the 2021 amendment to the same law, in addition to the obligation to ensure employment up to the age of 65 years, attempted to raise the retirement age to 70 years, introduce a continuous employment system, or abolish the mandatory retirement age, limited evidence has been collected on the employment status of older nurses by facility (*19-21*). To ensure effective employment continuity measures in Japan, facilities that employ nurses aged ≥ 55 years should first be identified.

In Japan, as of 2020, more than 90% of nurses aged ≤ 29 years and 75-80% of nurses in their 30s were employed in hospitals. However, as nurses age, the proportion working in hospitals decreases. Nurses in their 40s increasingly work in non-hospital settings, such as clinics, long-term care insurance facilities (LTCIFs), and home-visit nursing agencies (VNAs). By their 50s, more than half are employed in these non-hospital settings (*22*). However, existing surveys primarily focus on individual nurses, leaving a gap in understanding the broader employment landscape for older nurses. Therefore, this study aimed to: 1) provide a comprehensive overview of the proportion of older nursing staff aged ≥ 55 years employed across various facilities in Japan and 2) explore the factors associated with the percentage of older nursing staff at the facility level.

Materials and Methods

Study design and participants

This nationwide descriptive cross-sectional study was conducted between January and March 2022. The focus was on four specific types of facilities in Japan: hospitals, bedded clinics, LTCIFs, and VNAs. Stratified random sampling was employed, considering a skewed distribution based on the number of facilities per prefecture for each facility type; thus, there were 2,000 cases across a total of 8,000 facilities.

A list of addresses for each facility was obtained from the Local Health and Welfare Bureau (as of October 1, 2021) and the Ministry of Health, Labour and Welfare (MHLW) *via* their websites (as of June 30, 2021). Excluding inactive facilities, the list included 8,164 hospitals, 6,202 bedded clinics, 14,362 VNAs, and 12,812 LTCIFs. LTCIFs, in particular, included 7,895 welfare facilities, 4,184 healthcare facilities, and 733 sanatorium-type medical care facilities for older adults requiring long-term care.

Data were collected using anonymous, self-administered questionnaires sent to each facility's nursing director. A cover letter explaining the study's aim and ethical considerations was attached, along with a return envelope. Additionally, a reminder letter was sent three weeks after the initial survey was mailed.

Types of target facilities

The four types of facilities investigated were hospitals, bedded clinics, LTCIFs, and VNAs. At the time, more than 1.2 million nurses were employed across Japan, 69% of whom were employed in hospitals, 13.2% in clinics, 7.9% in LTCIFs, and 4.9% in VNAs. These facilities had the highest number of nurses employed, as indicated by statistics published by the MHLW (*12*). Given that nursing care is required in these facilities, staffing standards were established by law for each facility.

Hospitals

Hospitals in Japan are classified into various types according to their specialized services, sizes, and functions. This study included all hospital types.

Bedded clinics

Clinics are categorized into bedded and non-bedded clinics. The former refers to small medical facilities with ≤ 19 beds that provide outpatient and inpatient care and are staffed by nursing personnel. The latter focuses solely on outpatient care and therefore does not follow nursing staffing standards. To clarify the actual employment status of nursing staff, this study only included bedded clinics.

Long-term care insurance facilities (LTCIFs)

LTCIFs provide physical care, daily living assistance, and preventive care services required by older adults to perform daily activities. This includes welfare, healthcare, and convalescent care facilities and is based on the long-term care insurance system. However, medical insurance systems are only applied when medical services are provided.

Home-visit nursing agencies (VNAs)

VNAs provide nursing care, monitor health status, administer medications, impart health education, and coordinate care with other healthcare providers within the user's home. VNAs generally leverage benefits from either long-term care or health insurance depending on the user's condition and needs. Approximately half of all VNAs operate with fewer than five full-time nurses (*23*).

Instruments

The questionnaire comprised two main elements: organizational characteristics and number of nursing staff. The questionnaire items were created by referring to several previous studies and surveys (*21,22,24–28*). In

addition to the questionnaire, national public data were obtained to examine the regional characteristics of the facilities.

Organizational characteristics

Organizational characteristics included ownership, year of establishment, prefecture, and number of beds, residents, and users. From the obtained questionnaire data, the number of nursing staff per 100 beds was calculated for each hospital, and the number of nursing staff per 10 beds was calculated for bedded clinics and LTCIFs. Regarding VNAs, the number of users per nursing staff was calculated.

Number of nursing staff

The nursing staff were calculated according to job category (registered nurses, associate nurses, and nursing assistants) and job type (full-time or part-time). In this study, the number of nursing staff members reflected the combined number of registered and associate nurses. Nursing staff aged 55 years and older were surveyed in five-year age brackets (55-59, 60-64, 65-69, 70-74, 75-79, and ≥ 80 years) to determine their numbers by age. These numbers were then used to calculate the total number of nursing staff aged ≥ 55, ≥ 60, ≥ 65, ≥ 70, ≥ 75, and ≥ 80 years. The employment percentage of older nursing staff was calculated by dividing the number of staff aged ≥ 55, ≥ 60, and ≥ 65 years by the total number of nursing staff.

Prefecture characteristics

The following variables were used as regional characteristics: total population, percentage of population aged ≥ 65 years, number of hospitals per 100,000 population, number of bedded clinics per 100,000 population, number of LTCIFs per 100,000 population aged ≥ 65 years, and number of VNAs per 100,000 population aged ≥ 65 years. The total population and the percentage of population aged ≥ 65 years were obtained from the 2020 population census (*29*). The number of hospitals and bedded clinics was obtained from the Survey of Medical Institutions, and the number of LTCIFs and VNAs was obtained from the Survey of Institutions and Establishments for Long-Term Care (*30*).

Statistical analysis

Descriptive statistics were calculated for each facility, considering the organizational characteristics and employment status of the nursing staff. Kruskal–Wallis or χ^2 tests were conducted to evaluate the differences between the facilities. A violin plot was prepared to depict the percentage of older nursing staff by age group. The violin plot depicted the volume of samples at each point by width, with lines corresponding to the 25th, median, and 75th percentiles.

Owing to the nature of data clustering within the region (prefecture), generalized estimating equation (GEE) models were used to examine the factors associated with the percentage of older nursing staff at the facility level. Univariate and multivariate GEE models were stratified by the type of facility, including hospitals, bedded clinics, LTCIFs, and VNAs. The following organizational and regional characteristics were selected as independent variables: total population; percentage of population aged ≥ 65 years; number of hospitals per 100,000 population; number of bedded clinics per 100,000 population; number of LTCIFs per 100,000 population aged ≥ 65 years; number of VNAs per 100,000 population aged ≥ 65 years; ownership; year of establishment; number of beds, residents, and users; number of nursing staff per 100 hospital beds, per 10 beds, and per 10 residents, and number of users per nursing staff (VNA); percentage of full-time nursing staff in all types of employment; and percentage of nurses among nursing staff. In Japan, although the retirement age system is being reconsidered and the age is gradually being raised, the actual retirement age is often 60 years old. Therefore, we used three dependent variables: cutoff ages of 55, 60, and 65 years. Multicollinearity in the models was assessed using calculated variance inflation factors (< 7). The *p*-value of significance was set at $p < 0.05$ (two-tailed). All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA), and R-4.3.0 was used to generate the figures.

Ethical considerations

This study was approved by the ethics review committee of the Institute for Integrated Education of Tokyo Medical and Dental University (no. C2021-005). Participation was voluntary, and the protection of private information and strict data handling were guaranteed. The participants provided consent by checking the research consent box on the questionnaire.

Results

In total, 2,438 questionnaires were collected from 8,000 facilities (response rate: 30.5%). After excluding 780 questionnaires due to lack of consent, missing data, unanswered questions, or errors, completed questionnaires from 1,658 facilities (valid response rate: 20.7%) were included in the analysis, representing 431 hospitals, 363 clinics, 451 LTCIFs, and 413 VNAs (Figure 1). The median (interquartile range [IQR]) number of beds, residents, and users was 134 (74-248) in hospitals, 17 (10-19) in bedded clinics, 86 (63-100) in LTCIFs, and 70 (50-110) in VNAs. The medians (IQR) of the number of nursing staff were 75 (42-156) in hospitals, 11 (6-17) in bedded clinics, 7 (5-11) in LTCIFs, and 6 (4-8) in VNAs. The proportion of nurses varied significantly across facility types, with the highest being 100% in VNAs and the lowest being 62.5% in LTCIFs (Table 1).

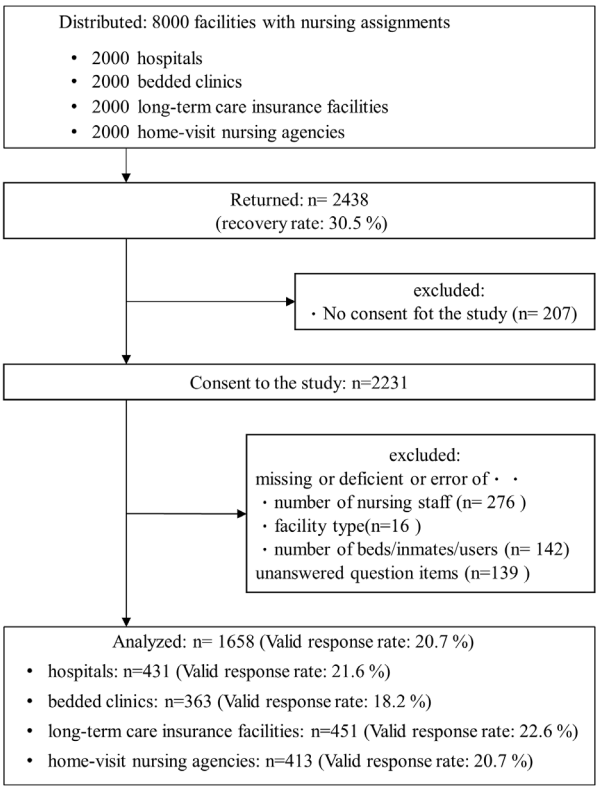

Figure 1. Selection flow of participating facilities.

Comparing the employment status of older nursing staff by facility types

The differences in the distribution of older nursing staff aged ≥ 55 years employed by facility type were statistically significant across all age groups ($p < 0.01$) (Figure 2). The percentage of older nursing staff employed in LTCIFs exceeded that of other facility types, followed by bedded clinics, VNAs, and hospitals. In the ≥ 55 years age group, clinics and VNAs had a median employment percentage of approximately 25%, whereas LTCIFs had a median employment percentage of approximately 45%. However, the distribution ranged from 0% to 100% and was slightly skewed. The proportion of older nursing staff employed in hospitals was distributed across a range of 0%-75%, with a monomodal right-skewed distribution of approximately 13%. When the cutoff age changed from ≥ 55 to ≥ 60 and ≥ 65 years, the percentage of older nursing staff decreased among all facility types. Although the mode for the percentage of nursing staff aged ≥ 65 years was 0%, 9.3% of the facilities had a percentage of 25% or more.

Factors associated with the percentage of older nurses

Univariate analysis results using GEE models showed that the factors associated with the percentage of older nursing staff aged ≥ 55 years differed across the four facility types: hospitals, bedded clinics, LTCIFs, and VNAs (Supplemental Tables S1-S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=86*). In the case of hospitals, a higher proportion of older staff was associated with a lower number of beds (coef. = -0.02 to -0.01, 95% CI: -0.03 to 0.00, $p < 0.01$), a lower number of staff per 100 beds (coef. = -0.17 to -0.06, 95% CI: -0.22 to -0.04, $p < 0.01$), a lower percentage of full-time nursing staff (coef. = -0.31 to -0.12, 95% CI: -0.43 to -0.03, $p < 0.01$), a lower percentage of nurses among nursing staff (coef. = -0.58 to -0.22, 95% CI: -0.65 to -0.18, $p < 0.01$), and a lower total population (coef. = -0.08 to -0.05, 95% CI: -0.12 to -0.02, $p < 0.01$); these negative associations were consistently observed across all age categories. (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=86*). In bedded clinics, a positive association with the number of beds was found only in the ≥ 65 years age group (coef. = 0.17, 95% CI: 0.01 to 0.33, $p = 0.03$), while the association with prefecture variables was minimal (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=86*). In the case of LTCFs, an association with the number of nursing staff per 10 residents was found only in the ≥ 65 years age group (coef. = 1.13, 95% CI: -2.07 to -0.18, $p = 0.02$) (Supplemental S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=86*). Finally, in VNAs, an association with the percentage of full-time nursing staff in all types of employment was found only in the ≥ 65 years age group (coef. = -0.07, 95% CI: -0.12 to -0.02, $p < 0.01$) (Supplemental S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=86*).

Multivariate analysis using GEE models stratified by facility types revealed that the higher percentage of older nursing staff aged 55 years and older was negatively associated with ownership by a non-profit medical corporation (coef. = -3.96, 95% CI: -6.50 to -1.42, $p < 0.01$), number of beds (coef. = -0.01, 95% CI: -0.01 to -0.00, $p = 0.03$), number of nursing staff per 100 beds (coef. = -0.08, 95% CI: -0.12 to -0.03, $p < 0.01$), full-time nursing staff in all types of employment (%) (coef. = -0.20, 95% CI: -0.30 to -0.10, $p < 0.01$), and nurses among nursing staff (%) (coef. = -0.49, 95% CI: -0.59 to -0.39, $p < 0.01$) in hospitals. No association with prefecture variables was found for all four facility types for the percentage of nursing staff aged ≥ 55 years (Table 2).

When the age category was set to ≥ 60 years, the same trend was observed in the association with the percentage of older nursing staff. However, an association with the total population, which is a prefectural characteristic, was observed only in bedded clinics (coef. = 0.18, 95% CI: 0.05 to 0.31, $p < 0.01$) and VNAs (coef. = 0.08, 95% CI: 0.01 to 0.16, $p = 0.04$) (Table 3).

Regarding the percentage of nursing staff aged ≥

Table 1. Descriptive statistics of organizational characteristics according to total and facility type (*n* = 1,658)

Variable	By category				*p*-value†
	Hospital (*n* = 431)	Bedded clinic (*n* = 363)	Long-term care insurance facility (*n* = 451)	Home-visit nursing agency (*n* = 413)	
Ownership, *n* (%)					
National	12 (2.8)	0 (0.0)	0 (0.0)	1 (0.2)	< 0.001
Public medical institution	79 (18.3)	6 (1.7)	18 (4.0)	18 (4.4)	
Social insurance group	6 (1.4)	2 (0.6)	1 (0.2)	2 (0.5)	
Non-profit medical corporation	268 (62.2)	273 (75.2)	124 (27.5)	91 (22.0)	
Social welfare corporation	13 (3.0)	1 (0.3)	301 (66.7)	21 (5.1)	
For-profit corporation	0 (0.0)	0 (0.0)	0 (0.0)	202 (48.9)	
Private	5 (1.2)	71 (19.6)	0 (0.0)	24 (5.8)	
Other	48 (11.1)	10 (2.8)	7 (1.6)	54 (13.1)	
Year of establishment, Median (IQR)	1976 (1955–1991)	1994 (1981–2003)	1998 (1991–2006)	2016 (2007–2019)	< 0.001
Area, *n* (%)					
Hokkaido	34 (7.9)	21 (5.8)	18 (4.0)	25 (6.1)	< 0.001
Tohoku	39 (9.0)	41 (11.3)	56 (12.4)	30 (7.3)	
Kanto	103 (23.9)	57 (15.7)	123 (27.3)	114 (27.6)	
Chubu	69 (16.0)	54 (14.9)	68 (15.1)	57 (13.8)	
Kinki	70 (16.2)	28 (7.7)	76 (16.9)	86 (20.8)	
Chugoku/Shikoku	53 (12.3)	66 (18.2)	49 (10.9)	32 (7.7)	
Kyushu	63 (14.6)	96 (26.4)	61 (13.5)	69 (16.7)	
Number of beds/residents/users, Median (IQR)	134 (74-248)	17 (10-19)	86 (63-100)	70 (50-110)	< 0.001
Number of nursing staff, Median (IQR)	75 (42-156)	11 (6-17)	7 (5-11)	6 (4-8)	< 0.001
Percentage of nurses among nursing staff , Median (IQR)	90.0 (74.4-97.6)	66.7 (40.0- 83.3)	62.5 (45.5-78.8)	100 (90.0-100.0)	< 0.001
Percentage of full-time nursing staff in all types of employment, Median (IQR)	89.8 (82.4-95.2)	80.0 (60.0-100.0)	75.0 (57.1-100.0)	71.4 (50.0-100.0)	< 0.001
Number of nursing staff aged ≥ 55 years, Median (IQR)	12 (7-22)	3 (1-5)	3 (2-5)	1 (0-2)	< 0.001
Number of nursing staff aged ≥ 60 years, Median (IQR)	6 (3-10)	1 (0-2)	2 (1-3)	0 (0-1)	< 0.001
Number of nursing staff aged ≥ 65 years, Median (IQR)	1 (0-3)	0 (0-1)	0 (0-1)	0 (0-0)	< 0.001
Number of nursing staff aged ≥ 70 years, Median (IQR)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	< 0.001

†Kruskal–Wallis test was conducted for quantitative variables, and the χ^2 test was conducted for categorical variables. Abbreviations: IQR, interquartile range.

65 years, higher percentages of full-time employees and nurses in nursing staff were negatively associated with most facility types, while the number of beds was not associated with any facility type, except VNAs. Additionally, regarding prefectural characteristics, the total population was positively associated with the percentage of older nursing staff in bedded clinics (coef. = 0.07, 95% CI: 0.01 to 0.14, p = 0.03), whereas in LTCIFs, negative associations were found with the total population (coef. = -0.06, 95% CI: -0.10 to -0.01, p = 0.02) and the percentage of the population aged ≥ 65 years (coef. = -0.76, 95% CI: -1.43 to -0.08, p = 0.03). Furthermore, in bedded clinics, the number of VNAs per 100,000 population aged ≥65 years was negatively associated (coef. = -0.12, 95% CI: -0.22 to -0.01, p = 0.03), while it was positively associated in VNAs (coef. = 0.10, 95% CI: 0.00 to 0.20, p = 0.04) (Table 4).

Discussion

This nationwide survey depicted the distribution of facilities in Japan employing older nursing staff. The results revealed that LTCIFs employed the highest median percentage of older nursing staff in all considered age groups (≥ 55 years, ≥ 60 years, and ≥ 65 years), followed by clinics, VNAs, and hospitals. Additionally, the percentage of nurses among nursing staff in the facilities and the number of full-time employees in the nursing staff were negatively associated with the percentage of older nursing staff in the facilities.

Although the biennial survey conducted by the MHLW reported the number of employed nurses by age group, this study was significant in that it showed employment trends for nursing staff in a facility. In a previous study, 21.8% of the total number of older nursing staff were aged ≥ 55 years, and 11.8% were aged ≥ 60 years (*22*). Conversely, this study found that some facilities, such as LTCIFs, VNAs, bedded clinics, and hospitals (particularly, smaller ones), rely on a workforce aged 55 to 60 years and older. Owing to the overall aging of the nursing workforce, this group may experience workforce shortages in the near future because of

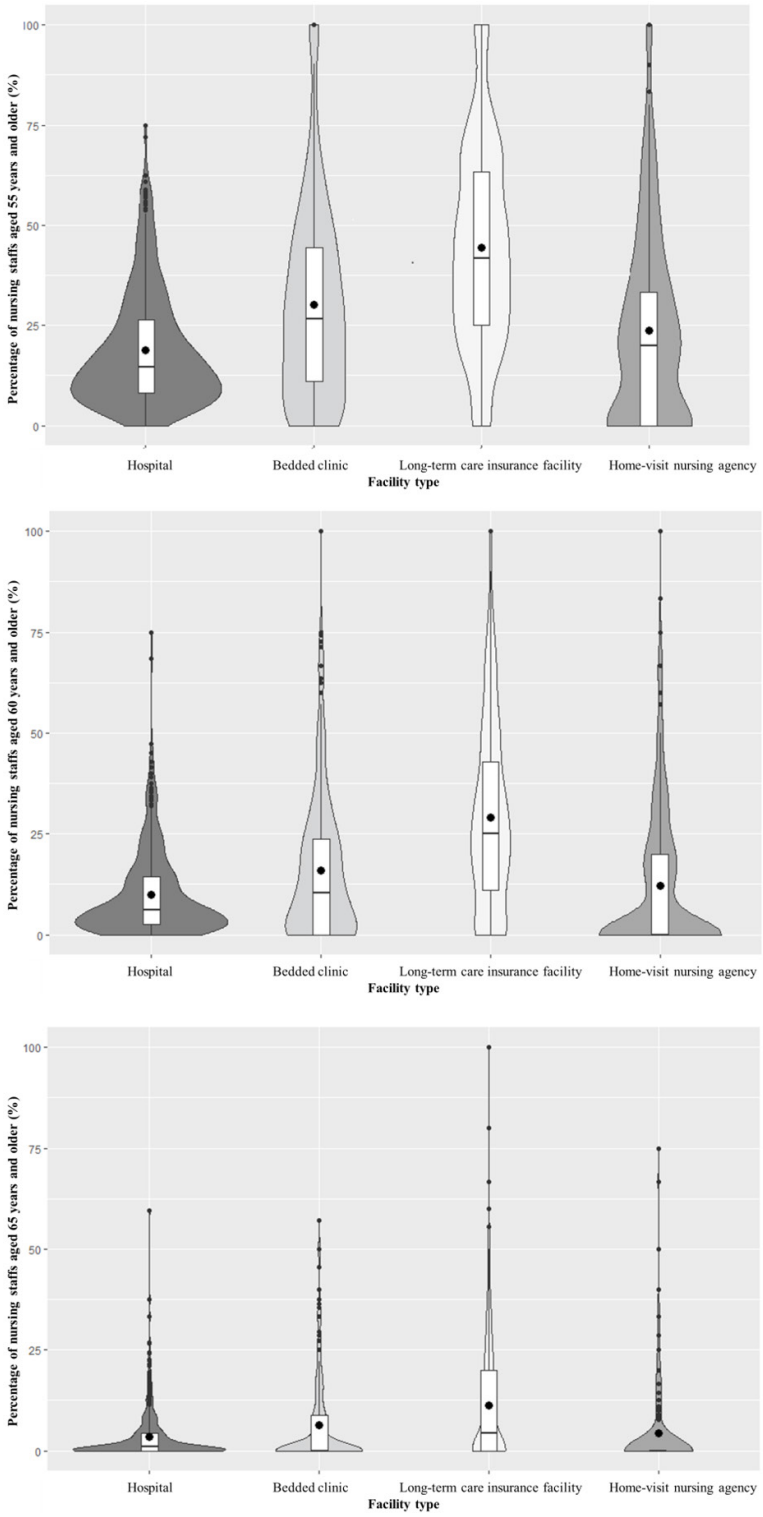

Figure 2. Violin plots showing the percentage of older nursing staff employed by facility type and age group. These plots show the sample size at each point in terms of width, with lines corresponding to the 25th percentile, median, and 75th percentile and dots corresponding to the mean. Kruskal–Wallis test results showed statistically significant differences between facilities concerning the percentage of older nursing staff employed based on all age groups ($p < 0.001$).

retirement and age-related departures. Based on this, strategies should be implemented to ensure that older nurses can work beyond the retirement age. Furthermore, in facilities with a high proportion of older nursing staff, the specific skills and working conditions required by managers must be further explored and clarified. By considering ways to match job seekers with managers' needs, stable nursing care can be provided.

Furthermore, this study also found that facilities with higher percentages of nurses among the nursing staff and those with a higher percentage of full-time employees among the nursing staff were less likely to employ older

Table 2. Generalized estimating equations results for the percentage of nursing staff aged 55 years and older by facility type

	Hospital				Bedded clinic				Long-term care insurance facility				Home-visit nursing agency			
	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*
(Intercept)	109.34	32.48	45.67 - 173.00	< 0.01*	79.90	167.60	-248.58 - 408.38	0.63	455.62	166.53	129.23 - 782.01	< 0.01*	790.08	317.89	167.03 - 1413.12	0.01*
Facility characteristics																
Ownership (ref. Other)																
Non-profit medical corporation	-3.96	1.30	-6.50 - -1.42	< 0.01*	-5.33	3.00	-11.22 - 0.56	0.08								
Social welfare corporation									1.85	2.02	-2.10 - 5.80	0.36				
For-profit corporation													1.53	2.24	-2.86 - 5.92	0.49
Year of establishment	-0.01	0.02	-0.04 - 0.02	0.51	-0.03	0.09	-0.20 - 0.14	0.72	-0.19	0.09	-0.36 - -0.03	0.02*	-0.39	0.15	-0.69 - -0.08	0.01*
Number of beds/residents/users	-0.01	0.00	-0.01 - 0.00	0.03*	-0.32	0.31	-0.93 - 0.28	0.30	-0.07	0.03	-0.13 - -0.01	0.02*	-0.07	0.02	-0.10 - -0.04	< 0.01*
Number of nursing staff per 100 beds	-0.08	0.02	-0.12 - -0.03	< 0.01*												
Number of nursing staff per 10 beds/residents					-0.10	0.08	-0.26 - 0.06	0.24	-2.10	0.92	-3.90 - -0.29	0.02*				
Number of users per nursing staff													0.12	0.13	-0.13 - 0.36	0.35
Percentage of full-time nursing staff in all types of employment	-0.20	0.05	-0.30 - -0.10	< 0.01*	-0.11	0.07	-0.24 - 0.03	0.12	-0.18	0.05	-0.29 - -0.08	< 0.01*	-0.02	0.05	-0.11 - 0.07	0.69
Percentage of nurses among nursing staff	-0.49	0.05	-0.59 - -0.39	< 0.01*	-0.29	0.05	-0.39 - -0.18	< 0.01*	-0.19	0.05	-0.29 - -0.08	< 0.01*	-0.32	0.06	-0.45 - -0.20	< 0.01*
Prefectural characteristics																
Total population (100,000 persons)	-0.01	0.02	-0.06 - 0.04	0.67	0.12	0.10	-0.07 - 0.31	0.21	-0.07	0.04	-0.15 - 0.01	0.10	0.07	0.06	-0.04 - 0.19	0.20
Percentage of population aged ≥ 65	-0.24	0.31	-0.85 - 0.37	0.44	1.19	0.91	-0.59 - 2.96	0.19	0.60	0.73	-0.84 - 2.04	0.41	0.95	0.82	-0.67 - 2.56	0.25
Number of hospitals per 100,000 population	0.50	0.36	-0.20 - 1.21	0.16	-0.55	1.07	-2.65 - 1.55	0.61	-0.50	0.87	-2.19 - 1.20	0.57	-0.58	1.06	-2.65 - 1.50	0.59
Number of bedded clinics per 100,000 population	-0.22	0.18	-0.57 - 0.13	0.21	0.28	0.62	-0.94 - 1.49	0.65	-0.34	0.61	-1.55 - 0.86	0.57	0.68	0.76	-0.82 - 2.17	0.38
Number of LTCFs per 100,000 population aged ≥ 65	0.10	0.15	-0.19 - 0.39	0.51	0.06	0.38	-0.68 - 0.81	0.87	-0.19	0.24	-0.65 - 0.27	0.41	0.38	0.43	-0.46 - 1.23	0.38
Number of VNAs per 100,000 population aged ≥ 65	-0.05	0.06	-0.16 - 0.06	0.38	0.19	0.17	-0.14 - 0.52	0.26	0.13	0.13	-0.13 - 0.38	0.33	0.00	0.15	-0.29 - 0.30	0.99
(Scale)	107.55				540.50				598.95				524.53			

Dependent variable: Percentage of nursing staff aged 55 years and older among all staff. Results were based on generalized estimating equations. Each independent variable's regression coefficient (coef.), standard error (SE), and *p*-value (*p*) were reported. *$p < 0.05$ (statistical significance level). Additionally, 95% confidence intervals (CIs) were provided. Adjustments for clustering by prefecture and robust estimation were applied. Abbreviations: LTCF, Long-term care insurance facility; VNA, Home-visit nursing agency.

Table 3. Generalized estimating equations results for the percentage of nursing staff aged 60 years and older by facility type

	Hospital				Bedded clinic				Long-term care insurance facility				Home-visit nursing agency			
	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*
(Intercept)	81.41	22.93	36.47 - 126.36	< 0.01*	152.54	107.21	-57.60 - 362.67	0.16	194.18	167.01	-133.16 - 521.52	0.25	122.43	146.66	-165.02 - 409.88	0.40
Facility characteristics																
Ownership (ref. Other)																
Non-profit medical corporation	-1.05	1.10	-3.20 - 1.10	0.34	-1.65	2.08	-5.73 - 2.43	0.43								
Social welfare corporation									1.69	1.83	-1.89 - 5.27	0.35				
For-profit corporation													2.06	1.53	-0.95 - 5.06	0.18
Year of establishment	-0.01	0.01	-0.03 - 0.01	0.28	-0.06	0.05	-0.17 - 0.04	0.23	-0.06	0.08	-0.23 - 0.10	0.46	-0.06	0.07	-0.21 - 0.08	0.38
Number of beds/residents/users	0.00	0.00	0.00 - 0.00	0.77	-0.29	0.20	-0.68 - 0.11	0.15	-0.06	0.03	-0.11 - -0.01	0.03*	-0.04	0.01	-0.06 - -0.02	< 0.01*
Number of nursing staff per 100 beds	-0.05	0.01	-0.07 - -0.02	< 0.01*												
Number of nursing staff per 10 beds					-0.12	0.05	-0.22 - -0.03	0.01*	-1.61	1.03	-3.62 - 0.40	0.12				
Number of users per nursing staff													0.02	0.06	-0.11 - 0.14	0.80
Percentage of full-time nursing staff in all types of employment	-0.11	0.05	-0.21 - -0.02	0.02*	-0.13	0.05	-0.24 - -0.03	0.01*	-0.22	0.06	-0.33 - -0.11	< 0.01*	-0.06	0.03	-0.11 - 0.00	0.04
Percentage of nurses among nursing staff	-0.40	0.04	-0.48 - -0.31	< 0.01*	-0.17	0.04	-0.24 - -0.10	< 0.01*	-0.18	0.05	-0.27 - -0.08	< 0.01*	-0.19	0.06	-0.31 - -0.07	< 0.01*
Prefectural characteristics																
Total population (100,000 persons)	0.00	0.01	-0.02 - 0.03	0.77	0.18	0.06	0.05 - 0.31	< 0.01*	-0.05	0.05	-0.16 - 0.05	0.32	0.08	0.04	0.01 - 0.16	0.04*
Percentage of population aged ≥ 65	-0.20	0.17	-0.53 - 0.12	0.22	0.21	0.63	-1.03 - 1.46	0.74	-0.07	0.59	-1.22 - 1.08	0.91	0.94	0.70	-0.43 - 2.30	0.18
Number of hospitals per 100,000 population	0.24	0.23	-0.22 - 0.70	0.31	-0.36	0.71	-1.74 - 1.02	0.61	0.52	0.67	-0.80 - 1.84	0.44	-0.63	0.86	-2.31 - 1.05	0.46
Number of bedded clinics per 100,000 population	-0.10	0.15	-0.39 - 0.18	0.47	0.54	0.39	-0.22 - 1.29	0.16	-0.30	0.45	-1.18 - 0.57	0.50	0.05	0.51	-0.95 - 1.06	0.92
Number of LTCFs per 100,000 population aged ≥ 65	0.13	0.10	-0.08 - 0.33	0.23	0.26	0.27	-0.27 - 0.79	0.33	-0.18	0.22	-0.60 - 0.25	0.42	0.41	0.26	-0.09 - 0.91	0.11
Number of VNAs per 100,000 population aged ≥ 65	-0.05	0.04	-0.12 - 0.02	0.14	-0.24	0.13	-0.49 - 0.02	0.07	0.01	0.13	-0.24 - 0.27	0.91	0.00	0.08	-0.15 - 0.15	0.98
(Scale)	56.74				273.88				501.12				295.07			

Dependent variable: Percentage of nursing staff aged 60 years and older among all staff. Results were based on generalized estimating equations. Each independent variable's regression coefficient (coef.), standard error (SE), and *p*-value (*p*) were reported. *$p < 0.05$ (statistical significance level). Additionally, 95% confidence intervals (CIs) were provided. Adjustments for clustering by prefecture and robust estimation were applied. Abbreviations: LTCF, Long-term care insurance facility; VNA, Home-visit nursing agency.

Table 4. Generalized estimating equations results for the percentage of nursing staff aged 65 years and older by facility type

	Hospital				Bedded clinic				Long-term care insurance facility				Home-visit nursing agency			
	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*	coef.	SE	95% CI	*p*
(Intercept)	44.96	16.33	12.95 - 76.97	< 0.01*	117.28	56.29	6.94 - 227.61	0.04*	193.22	98.59	0.01 - 386.45	0.05	101.68	82.96	-60.92 - 264.27	0.22
Facility characteristics																
Ownership (ref. Other)																
Non-profit medical corporation	-0.37	0.86	-2.06 - 1.33	0.67	-3.89	1.69	-7.21 - -0.57	0.02*								
Social welfare corporation									1.26	1.09	-0.86 - 3.39	0.24				
For-profit corporation													1.45	0.90	-0.32 - 3.22	0.11
Year of establishment	-0.01	0.01	-0.02 - 0.01	0.26	-0.05	0.03	-0.11 - 0.00	0.07	-0.07	0.05	-0.17 - 0.03	0.15	-0.04	0.04	-0.12 - 0.03	0.27
Number of beds/residents/users	0.00	0.00	0.00 - 0.00	0.33	0.20	0.08	0.04 - 0.36	0.02*	-0.01	0.01	-0.04 - 0.02	0.61	-0.01	0.01	-0.02 - 0.00	0.01*
Number of nursing staff per 100 beds	-0.02	0.01	-0.03 - 0.00	0.05												
Number of nursing staff per 10 beds/residents					0.02	0.03	-0.05 - 0.08	0.61	-1.21	0.52	-2.23 - -0.20	0.02*				
Number of users per nursing staff													0.02	0.02	-0.02 - 0.07	0.34
Percentage of full-time nursing staff in all types of employment	-0.08	0.04	-0.16 - 0.00	0.05	-0.10	0.03	-0.16 - -0.03	< 0.01*	-0.19	0.04	-0.26 - -0.11	< 0.01*	-0.06	0.02	-0.10 - -0.02	< 0.01*
Percentage of nurses among nursing staff	-0.19	0.03	-0.25 - -0.14	< 0.01*	-0.09	0.02	-0.13 - -0.04	< 0.01*	-0.10	0.04	-0.18 - -0.03	< 0.01*	-0.15	0.05	-0.25 - -0.04	0.01*
Prefectural characteristics																
Total population (100,000 persons)	0.01	0.01	-0.01 - 0.03	0.24	0.07	0.03	0.01 - 0.14	0.03*	-0.06	0.02	-0.10 - -0.01	0.02*	0.01	0.03	-0.05 - 0.07	0.76
Percentage of population aged ≥ 65	-0.13	0.10	-0.31 - 0.06	0.19	0.05	0.40	-0.73 - 0.84	0.89	-0.76	0.34	-1.43 - -0.08	0.03*	-0.21	0.42	-1.04 - 0.62	0.62
Number of hospitals per 100,000 population	0.16	0.16	-0.15 - 0.47	0.31	-0.35	0.44	-1.22 - 0.52	0.43	0.09	0.58	-1.05 - 1.23	0.88	-0.11	0.41	-0.91 - 0.70	0.80
Number of bedded clinics per 100,000 population	-0.14	0.08	-0.30 - 0.03	0.10	0.46	0.24	-0.01 - 0.92	0.05	-0.17	0.28	-0.71 - 0.37	0.54	-0.04	0.26	-0.55 - 0.48	0.89
Number of LTCFs per 100,000 population aged ≥ 65	0.08	0.06	-0.05 - 0.20	0.24	0.08	0.14	-0.19 - 0.35	0.56	0.13	0.14	-0.15 - 0.41	0.35	0.26	0.17	-0.07 - 0.58	0.12
Number of VNAs per 100,000 population aged ≥ 65	-0.04	0.02	-0.08 - 0.01	0.12	-0.12	0.05	-0.22 - -0.01	0.03*	-0.01	0.08	-0.16 - 0.15	0.95	0.10	0.05	0.00 - 0.20	0.04*
(Scale)	25.30				104.70				205.21				120.82			

Dependent variable: Percentage of nursing staff aged 65 years and older among all staff. Results were based on generalized estimating equations. Each independent variable's regression coefficient (coef.), standard error (SE), and *p*-value *(p)* were reported. *p <0.05 (statistical significance level). Additionally, 95% confidence intervals (CIs) were provided. Adjustments for clustering by prefecture and robust estimation were applied. Abbreviations: LTCF, Long-term care insurance facility; VNA, Home-visit nursing agency.

nursing staff, at all cut-offs of ≥ 55 years, ≥ 60 years, and ≥ 65 years. This finding was consistent with the results of previous studies (*22,31*). The number of associate nurses in training is declining, and the workforce is aging. Additionally, they are more often employed on a part-time basis compared to nurses. Consequently, facilities that employ a large number of assistant nurses may be concerned about an aging workforce and the challenges of securing nursing staffs. Negative associations with the number of beds and staffing levels may stem from training programs in large hospitals and VNAs, which attract younger nursing staff who tend to prefer these settings. The negative correlation with years of establishment and the number of beds in LTCIFs and VNAs may be due to the small number of nursing staff who continue to work. On the contrary, the association between regional variables and the percentage of employees aged ≥ 55 years and those ≥ 60 years was minimal. Based on this, future research should consider the supply and demand of nursing staff and the age of working nursing staff at the secondary medical care level, which serves as a general unit for healthcare provision, rather than at the prefectural level.

Notably, some facilities employed a certain percentage of nursing staff aged > 65 years. Currently, policies are being implemented to promote home healthcare and long-term care services to meet the growing demand for nursing and long-term care, prioritizing the need to secure human resources (*19,32-34*). However, an association was observed between the percentage of nursing staff aged ≥ 65 years in bedded clinics and LTCIFs, and regional variables such as total population warrant consideration. Delaying the retirement of older nursing staff affects the overall supply of the nursing workforce (*35*). Policies to address the concurrent retirement of an aging nursing workforce should consider the impact of facilities that employ a high proportion of older nurses.

This study had several limitations. First, owing to the stratified random sampling of facilities nationwide, it did not constitute a complete survey. However, the distribution of the number of beds across the surveyed facilities was similar to that of the national data and may be somewhat representative. Second, the employment percentage of older nursing staff was used as the primary outcome variable. Therefore, the results should be interpreted with caution, particularly for facilities with a small overall number of employees such as VNAs, owing to the high per capita rate. Third, this study did not examine the reasons for hiring older nursing staff. Nursing staff well beyond retirement age may continue to be employed not only to secure human resources but also because they are expected to be highly proficient in their jobs. Further studies are required to examine this phenomenon.

Future studies should clarify the characteristics of facilities with a higher percentage of older nurses, as revealed in this study. The results of this study can serve as important material for policies that consider the impact of employing older nurses to secure human resources in Japan, where increased demand for medical and long-term care services is expected.

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Effects of low-frequency ultrasound combined with microbubbles on breast cancer xenografts in nude mice

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Abstract: The aim of this study was to explore the effects of low-frequency ultrasound (US) combined with microbubbles (MBs) on breast cancer xenografts and explain its underlying mechanisms. A total of 20 xenografted nude mice were randomly divided into four groups: a group treated with US plus MBs (the US + MBs group), a group treated with US alone (the US group), a group treated with MBs alone (the MBs group), and a control group. In different groups, mice were treated with different US and injection regimens on an alternate day, three times in total. Histological changes, apoptosis of cells, microvascular changes, and the apoptosis index (AI) and microvascular density (MVD) of the breast cancer xenograft were analyzed after the mice were sacrificed. Results indicated that the tumor volume in the US + MBs group was smaller than that in the other three groups ($p < 0.001$ for all). The rate of tumor growth inhibition in the US + MBs group was significantly higher than that in the US and MBs groups ($p < 0.001$ for both). There were no significant differences in histological changes among the four groups. However, the AI was higher in the US + MBs group than that in the other three groups while the MVD was lower ($p < 0.001$ for all). All in all, low-frequency US combined with MBs can effectively slow down the growth of breast cancer in nude mice. In summary, low-frequency US combined with MBs has a significant effect on breast cancer treatment. Cavitation, thermal effects, and mechanical effects all play a vital role in the inhibition of tumor growth.

***Keywords*:** low-frequency ultrasound irradiation treatment, nude mouse xenograft model of breast cancer, ultrasonic cavitation

Introduction

Worldwide, female breast cancer was the most common cancer with around 2.3 million new cases (11.7%) and the fifth leading cause of cancer death with around 0.7 million new deaths (*1*). Although more new cases were diagnosed in women over the age of 50, its incidence in younger women is rising (*2*). In China, breast cancer was the most common cause of cancer death (16.7%) in women ages 15-44 (*3*). Screening technology is becoming more mature and widespread, and more breast cancers of a smaller volume are detected at an even earlier stage (*4*). Therefore, early diagnosis and appropriate treatment affect patient prognosis. With the spread of breast-conserving surgery and the widespread use of pre- and postoperative adjuvant therapy, local treatment of breast cancer is developing rapidly (*5*). According to different tumor types and stages, different local treatments can be selected, such as radiotherapy (*6*), radiofrequency ablation (*7*), and microwave ablation (*8*).

Ultrasound (US) is now one of the hot fields in treating solid tumors. Bioeffects of US mainly consist of thermal effects, cavitation, and mechanical effects. High-intensity focused ultrasound (HIFU), as a therapy with thermal effects, has been used clinically to treat various solid tumors, like liver cancer and thyroid cancer (*9,10*). However, HIFU is still not widely used in breast cancer due to technical and equipment limitations, and it has a variety of complications, such as pain, skin burns, edema of the lungs, and major pectoralis injury. As a non-thermal therapy, low-frequency US has been widely studied in promoting cell apoptosis *in vitro* and *in vivo* (*11-14*). Cavitation plays an essential role in the inhibition of tumor growth by low-frequency US. According to the state of MB motion, cavitation is divided into stable cavitation and inertial cavitation; in the former, MBs move in

periodic, nonlinear oscillations under the action of periodically varying US. In the latter, MBs periodically expand and contract until they burst, releasing large amounts of energy. Low-frequency US has not been studied in depth in terms of its efficacy and mechanism of action in breast cancer. In our previous work, we found that the most suitable exposure parameters were a frequency of 1 MHz, an intensity of 2 W/cm^2, a duty cycle of 50%, and an exposure time of 5 min. The aim of the current study was to explore the effects of low-frequency US combined with MBs and explain its underlying mechanisms.

Materials and Methods

Cell culture

MDA-MB-231 cells (Shanghai Cancer Institute) were cultured in a RPMI-1640 medium (Gibco, America) supplemented with 10% of FBS (HyClone, US) at 37°C in an atmosphere of humidified 5% CO2. All experiments were performed in accordance with the requirements of the Guidelines for the Care and Use of Laboratory Animals and were approved by the Animal Experiment Ethics Committee of Shanghai Medical College of Fudan University.

Xenograft model establishment and sample collection

Female Balb/c nude mice (4-5 weeks old, 18-24 g) were acquired from Shanghai Xipur-Bikai Experimental Animal Co. Mice were bred under special pathogen-free (SPF) conditions.

When MDA-MB-231 cells reached the logarithmic phase, they were digested with a 0.25% EDTA trypsin digestive solution (Gibco, America), suspended, and harvested by centrifugation at 1,200 rpm for 5 min. A total of 1×10^6 cells suspended in 100 μL of PBS were injected subcutaneously under the second pair of right mammary fat pads of each nude mouse. After injection, the tumor growth was observed, and on the 10th day, the tumor grew to 10 mm, and the xenograft model was successfully established.

US treatment procedures

The US750 low-frequency ultrasonic therapeutic instrument (ITO Co. Ltd., Japan) was used in this study. US exposure was as follows: a frequency of 1 MHz, an intensity of 2 W/cm^2, a duty cycle of 50%, and exposure time of 5 min. SonoVue (Bracco, Milan, Italy), which contained sulfur hexafluoride gas and had a phospholipid monolayer shell, was shaken with 5 mL of normal saline into a MB suspension, and 0.2 mL of the MB suspension was injected into the mouse via the tail vein.

A total of 20 xenografted nude mice were randomly divided into four groups. The US plus MBs (US + MBs) group was treated with MBs followed by US. The MBs group was treated with MBs combined with empty exposure. The US group was treated with saline followed by US. The control group was treated with saline combined with empty exposure. All of the mice had undergone US or empty irradiation on an alternate day, three times in total. After the third treatment, all mice were kept under SPF conditions for 6 days. Afterwards, all xenografted mice were sacrificed. The tumors were removed for observation and fixed in formalin for further study.

Measurement of tumor growth

The tumor volume was calculated with the following formula: Volume (V) = $(\pi \times a \times b^2)/6$. The length (a) and width (b) of tumors were measured before each irradiation and every other day after the last irradiation, six times in total. The following formula was used to calculate the rate of tumor growth inhibition (TGI): TGI (%) = $(1 - V/V_0) \times 100\%$. (V represented the final volume in treatment groups, and V_0 represented the final volume in the control group)

Hematoxylin and eosin (H&E) staining

The harvested tumor specimens were fixed in a 4% formalin solution for 24 h. The tissues were embedded in paraffin and then cut into 4-μm-thick sections. The sections were stained with H&E for pathological examination. A microscope was used to photograph the sections at ×400 magnification to observe the tumor tissue pathology and structural changes.

Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay

Using the In Situ Cell Death Detection Kit (POD, Roche company, Germany), apoptosis of the tumor cells was determined with TUNEL. Apoptotic cells with DNA fragmentation stained brown. Slides were counterstained with hematoxylin, and the apoptotic cells stained brownish-yellow. The total number of tumor cell nuclei and TUNEL-positive cell nuclei were counted (magnification, ×400). Eight high-magnification fields were analyzed in each section. The positive cells and total cells in every field were counted and then the apoptosis index (AI) was calculated using the following formula: AI = (Number of positive cells/Number of whole cells) × 100%. The AI of all eight fields was averaged as the AI for the section.

CD34 immunohistochemical staining

The paraffin sections were dewaxed. The tissue sections were incubated with 3% methanol hydrogen peroxide for 5 min at room temperature, washed with PBS

three times to block endogenous peroxidases, and then blocked with dilute goat serum at room temperature for 20 min to block nonspecific antigens. Then, the tissues were continuously incubated with CD34 antibodies overnight, secondary antibodies for 20 min, and the chromogenic agent for 20 min, followed by hematoxylin counterstaining, dehydration, and mounting. The nuclei and cytoplasm of vascular endothelial cells stained brownish-yellow. The sections were observed under 40× magnification to determine areas of high blood vessel density, *i.e.*, hot spots. The number of vessels in hot spots was counted under 400× magnification. After observing five hot spots, the microvascular density (MVD) was calculated.

Statistics

Quantitative data are expressed as the mean ± standard deviation. Differences between or within groups were tested using one-way analysis of variance (ANOVA), and differences in ratios were tested using a chi-squared test. A *P* value<0.05 indicated statistical significance, and a *p* value<0.001 indicated marked statistical significance. Statistical analysis was performed using the software SPSS 13.0.

Results

Low-frequency US combined with MBs inhibited tumor growth

Tumor growth was significantly inhibited in the US + MBs group. The tumor volume in the US+MBs group (0.961 ± 0.490 mm^3, $p < 0.001$) was smaller than that in the control (2.067 ± 0.281 mm^3, $p < 0.001$), MBs (1.949 ± 0.250 mm^3, $p < 0.001$), and US groups (1.542 ± 0.133 mm^3, $p < 0.001$), and the TGI in the US + MBs group (53.51%, $p < 0.001$) was greater than that in the MBs (10.98%, $p < 0.001$) and US groups (25.40%, $p < 0.001$). Compared to the control and MBs groups, the tumor volume in the US group was markedly smaller ($p < 0.05$ for both), and the TGI in the US group was higher than that in the MBs group ($p < 0.001$). There were no significant differences in the tumor volume in the control and MBs groups ($p > 0.05$). The trends in tumor growth in the four groups are shown in Figure 1. Tumor volumes and TGIs are shown in Table 1.

Low-frequency US combined with MBs reduced erythrocyte-filled vessels without other pathological changes

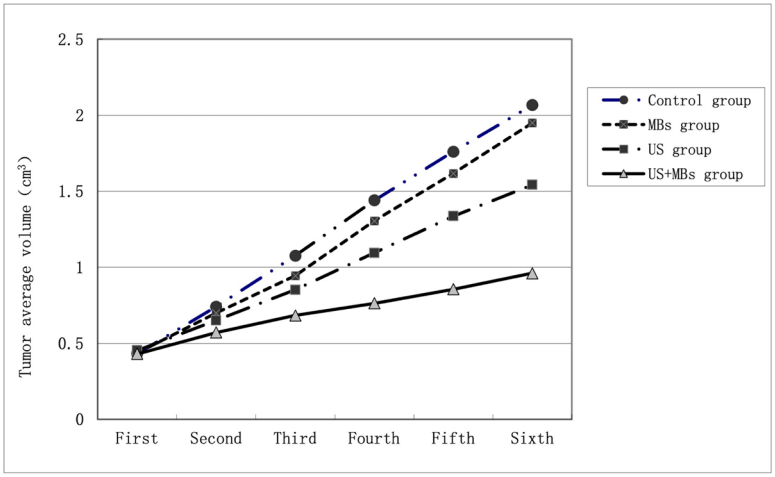

Figure 1. Growth trends for breast cancer xenografts. Tumor growth in the US + MBs group slowed down significantly and the slope was relatively slight. Tumor growth in the US group slowed down, and the slope was steeper than that in the US + MBs group. Trends in tumor growth were similar in the MBs and control groups, and the slopes were steep.

Table 1. Comparison of tumor growth in each group after treatment

Group	*n*	Tumor volume before treatment (mm^3)	Tumor volume before execution (mm^3)	TGI (%)
Control	5	0.434 ± 0.065	2.067 ± 0.281	-
MBs	5	0.437 ± 0.062	1.949 ± 0.250	10.98
US	5	0.454 ± 0.062	1.542 ± 0.133[a]	25.40[c]
US + MBs	5	0.431 ± 0.025	0.961 ± 0.490[b]	53.51[d]

(a) $p < 0.05$, US *vs*. Control, MBs, respectively; $p < 0.001$, US *vs.* US + MBs. (b) $p < 0.001$, US + MBs *vs.* Control, MBs, US, respectively. (c) $p < 0.001$, US *vs*. MBs. (d) $p < 0.001$, US + MBs *vs.* MBs, US, respectively. US: ultrasound; MBs: microbubbles; TGI: rate of tumor growth inhibition.

Pathological changes in tumor tissues are shown in Figure 2. H&E staining did not reveal noticeable histological differences in each group, and no apparent necrosis was observed. Under microscopic observation, the number of erythrocyte-filled vessels decreased in the US + MBs group compared to the other three groups. Erythrocyte leakage was seen in the interstitium in some areas in the US + MBs group.

Low-frequency US combined with MBs increased apoptosis

As shown in the TUNEL assay, the distribution of apoptotic cells in each group are shown in Figure 3. A few scattered stained apoptotic cells were seen in the control and MBs groups. In the US group, the number of apoptotic cells increased, and they were scattered. In the US + MBs group, apoptotic cells increased significantly, and they were present in sheets, and especially around blood vessels. The AI in the US + MBs group (49.02 ± 2.85%) was significantly higher than that in the other three groups (US: 11.04 ± 0.34%; MBs: 6.15 ± 0.29%; control: 4.68 ± 0.22%; $p < 0.001$ for all). The AI in the US group was markedly higher than that in the control and MBs groups ($p < 0.001$ for both). There were no significant differences in the AI in the MBs and control groups ($p > 0.05$). The AIs in the four group are shown in Table 2.

Low-frequency US combined with MBs reduced the microvascular density

After CD34 staining, the microvascular endothelium stained brownish-yellow, as shown in Figure 4. In the control and MBs groups, several microvessels were observed in areas where the tumor thrived. However, the number of microvessels decreased in the US group. In the US + MBs group, the number of microvessels decreased significantly, and the residual lumens were

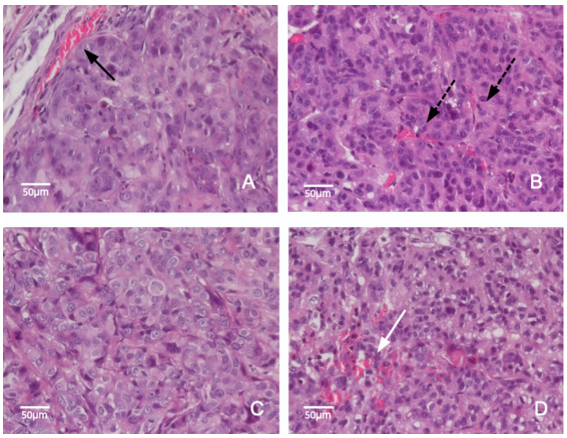

Figure 2. H&E staining of breast cancer xenografts (×400). (A) In the control group, donor blood vessels are visible at the edge of the tumor, and the lumen is filled with erythrocytes (black arrow). **(B)** In the MBs group, a few vessels are seen in the tumor, and a few erythrocytes are seen in the lumen (dotted arrow). **(C)** There are few vessels in the US group. **(D)** In the US + MBs group, erythrocytes leaked into the interstitium (white arrow). H&E: hematoxylin and eosin.

Table 2. Comparison of AI and MVD after treatment among groups

Group	*n*	AI (%)	MVD
Control	5	4.68 ± 0.22	10.93 ± 0.37
MBs	5	6.15 ± 0.29	10.48 ± 0.44
US	5	11.04 ± 0.34[a]	6.59 ± 0.24[a]
US + MBs	5	49.02 ± 2.85[b]	3.75 ± 0.36[b]

(a) $p < 0.001$, US *vs.* Control, MBs, US + MBs, respectively. (b) $p < 0.001$, US + MBs *vs.* Control, MBs, US, respectively. MVD: microvascular density; AI: apoptosis index; US: ultrasound; MBs: microbubbles.

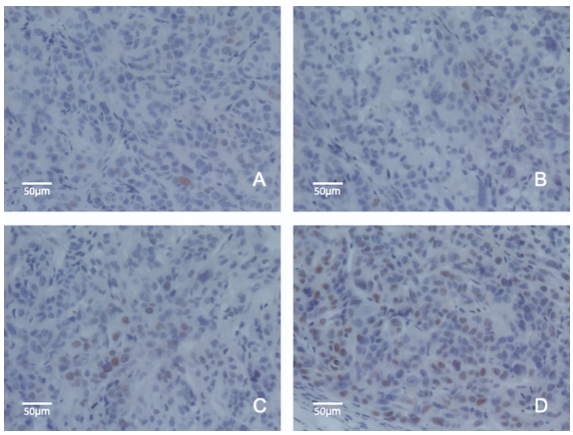

Figure 3. Tumor apoptosis after treatment in four groups (×400). (A) and **(B)** There were a few scattered apoptotic cells in the control and MBs groups. **(C)** Apoptotic cells increased and were scattered in the US group. **(D)** Apoptotic cells significantly increased and were present in sheets in the US + MBs group.

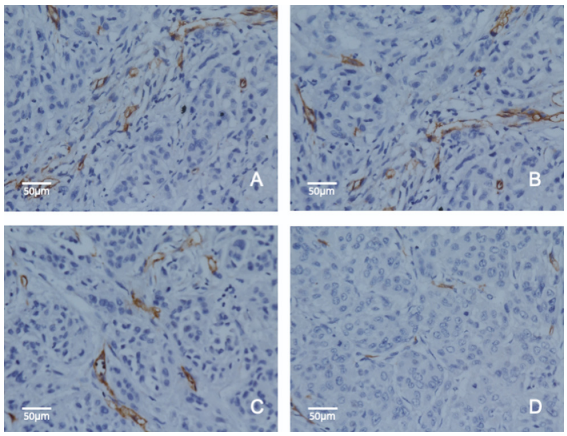

Figure 4. MVD after treatment in four groups (×400). (A) and **(B)** There are many microvessels in the control and MBs group. **(C)** Microvessels decreased slightly in the US group. **(D)** Microvessels decreased significantly in the US + MBs group, and the residual lumens are mostly closed. MVD: microvascular density.

mostly closed. MVD in the US group was lower than that in the control and MBs groups ($p < 0.001$). The MVD in the US + MBs group (3.75 ± 0.36) was markedly lower than that in the other three groups (US: 11.04 ± 0.34; MBs: 6.15 ± 0.29; and control: 4.68 ± 0.22; $p < 0.001$ for all). There were no significant differences in the MVD in the control and MBs groups ($p > 0.05$). The MVDs in the four groups are shown in Table 2.

Discussion

US is widely investigated and has developed in diagnostic and therapeutic fields, and low-frequency US is currently a topic of therapeutic study. Compared to high-frequency US, low-frequency US produces less heat and more cavitation. The ability of low-frequency US to inhibit tumor proliferation had been proved in several studies. Jang *et al*. observed cell death in melanoma cells mixed with Optison MBs after low-intensity US (*15*). Cao *et al*. found that low-intensity US suppressed the ability to proliferate, form colonies, and invade AsPC-1 cells (*11*). However, its clinical use in breast cancer *in vivo* is still unclear. The current study established a breast cancer model in nude mice and then subjected breast cancer xenografts to low-frequency US treatment combined with MBs. This study tried to clarify its clinical effects and discussed the underlying mechanisms.

Different US regimens can lead to different cell outcomes. When the frequency is fixed, total cell death and the ratio of necrosis increases with increasing intensity (*16*). In our previous study, we used different parameters for US (1 MHz) to treat breast cancer xenografts in nude mice. US at a frequency of 1 MHz, an intensity of 2 W/cm^2, and a duty cycle of 50% maximally inhibited tumor growth without the death of nude mice. With the current treatment, low-frequency US (a frequency of 1 MHz, an intensity of 2 W/cm^2, a duty cycle of 50%) significantly inhibited breast cancer xenografts, as evinced by the inhibition of tumor growth and abundant apoptotic cells, especially in the US + MBs group. Interestingly, there was no evidence of necrosis during the whole treatment. When tumors were treated with HIFU, significant coagulation necrosis may occur (*9,17*). The current study indicated that tumor destruction induced by low-frequency US was due to cell apoptosis, rather than cell necrosis.

When US irradiation at a specific frequency and intensity is applied to a liquid, cavitation nuclei will be created, followed by a change in volume, collapse, and a burst of the nuclei. Transient cavitation bubbles oscillate strongly and exist for only a few acoustic cycles, eventually collapsing, producing a large number of free radicals and a high local temperature and pressure (*18,19*). Oscillating bubbles also create microstreaming, which can induce shear stress on nearby cells or vessel endothelium (*20*). In addition, the force of radiation pushes bubbles towards the direction of wave propagation, which may have some impact on the endothelium. Actions on endothelium cause various stimuli, which are related to cell apoptosis alone or together, including damage to nuclear DNA (*21*), reactive oxygen species (*22*), a change in membrane permeability (*23*), disturbance of the calcium balance (*24,25*), and stimulation of the endoplasmic reticulum (*26*).

All of the above proved that cavitation-related effects lead to apoptosis. However, inducing cavitation in whole blood is not easy, probably because the body continuously filters impurities, including cavitation nuclei (*27*). SonoVue MBs were used as artificial cavitation nuclei, which markedly lowered the cavitation threshold and amplified the effect of US. Results indicated significantly better efficacy in the US + MBs group than that in the US group, which was confirmed in several other studies. Shen *et al.* used US at a frequency of 21 kHz on rabbit VX2 liver tumors, and the TGI was the highest in the US + MB group (*28*). Cao *et al.* indicated that US at a frequency of 45 kHz had the most efficient effect on decreasing cell viability and suppressing the ability of AsPC-1 cells to proliferate and form colonies in the US + MB group (*11*). However, comparing the efficacy of US across studies is not easy because different investigators used different US parameters and treatment conditions and acted on different targets.

In addition to cavitation, thermal effect is one of the essential bioeffects of low-frequency US. Mild hyperthermia can induce apoptosis in tumor cells and act synergistically with other therapies since it leads to several significant physiological changes by increasing the tumor blood flow and the perfused fraction of the tumor (*29-31*). When modulated electro-hyperthermia treatment was applied to the BALB/c mouse isograft model, the elevated expression of heat shock protein (HSP) 70 indicated heat shock-related cell stress, and the treated tumor showed significant signs of apoptosis and upregulation of caspase-3 (*32*). The stress protein response to US irradiation produced a large amount of HSPs, and elevated levels of HSP can trigger apoptosis (*32*). All of the above indicate that hyperthermia plays a certain role in oncotherapy. It has rarely been used clinically alone or with other therapies, so more research needs to be conducted in the future.

Neovascularization is associated with the reproduction, invasion, and metastasis of tumors. The destruction of supply vessels that provide sufficient oxygen and other nutrients to tumor cells can inhibit the growth of a tumor. The current study noted obvious vessel damage and erythrocyte leakage in the US + MBs group, which might be related to the cavitation and thermal effects of low-frequency US. Shock waves generated by MBs collapsing near the vessel wall may create liquid jets that damage endothelium and

cause holes in the vessel wall, activating coagulation and causing thrombosis (*33*). Shen *et al.* found that sonication with low-frequency US at 20 kHz and MBs of the rabbit carotid artery formed holes, local vascular wall defects, and arterial elastic membrane separation (*34*). Shen *et al.* indicated that diffused interstitial hemorrhages and vascular thrombi were observed after US treatment with MBs in rabbit VX2 hepatic tumors (*28*). The above studies indicated that low-frequency US combined with MBs can disrupt supply vessels, which may explain the inhibition of tumor growth.

Compared to vessels of normal tissue, tumor vessels are immature, abnormal, and highly permeable. Some large tumor vessels lack smooth muscle and are only consist of endothelium and a basement membrane. The endothelium in tumors is also structurally defective; it is discontinuous and full of gaps, causing hemorrhaging and facilitating permeability. Poorly differentiated cell contacts, abnormal cell-cell junctions, and exaggerated leakiness cause defects in endothelial cell barrier function (*35*). Tumor vessel density is very heterogeneous, and the arrangement of vessels is chaotic, especially in the center (*35*). Due to either increased endothelial permeability or tortuous vessels, the blood flow rate in tumor sites decreases, and MBs tend to be trapped at tumor sites rather than normal tissue sites. DeOre *et al*. found that the longer the residence time of MBs, the more sufficient thermal effects of damaging the endothelium (*36*). The difference in temperature enables the selective disruption of tumor blood vessels without causing a significant adverse effect on normal blood vessels (*37*).

In our study and other studies, low-frequency US has displayed a certain level of efficacy on solid tumors and no skin damage, death of mice, or metastasis were observed in our study, there are still concerns about the negative impact of using low-frequency US. For this reason, some researchers have discussed the possible negative effects of low-frequency US irradiation. Yang *et al.* found that after exposure to 0.6W/cm^2 for 15 minutes, epidermal and dermal necrosis, excoriation, and inflammatory cell infiltration were seen in skin tissue (*38*). While after exposure to 0.35W/cm^2 for 15 min, mouse skin displayed no obvious changes (*38*). Hence, at certain frequencies and intensities, US irradiation caused no significant damage to the skin of mice. Similarly, when controlled within a certain threshold, the effect of US irradiation on human skin is negligible (*39*). Although whether low-frequency US irradiation does harm to the surrounding normal tissues was not considered in our study, it has been determined by other researchers. Wang *et al.* treated mouse pancreatic cancer cells and normal pancreatic ductal epithelial cells with low-frequency US; with MB concentrations under 15%, the viability of normal pancreatic cells was not affected, while with MB concentrations under 30%, the rate of inhibition of pancreatic cancer cells increased progressively (*40*). The difference between normal cells and cancer cells when subjected to low-frequency US irradiation is closely related to apoptotic factors. For example, survivin is a member of the inhibitor of apoptosis protein family, which are selectively expressed in various malignant tumors but which are not expressed or which are expressed at lower levels in normal tissues (*41*). Under the action of low-frequency US, the up- and down-regulation of pro- and anti- apoptotic factors jointly leads to the apoptosis of cancer cells, thereby inhibiting the proliferation of cancer cells. Studies have shown that low-frequency US irradiation can inhibit the migration of cancer cells, thereby reducing the possibility of metastasis. In a study by Wei *et al*., low-frequency US was applied to prostate cancer cells, and cancer cell migration in the experimental group was significantly inhibited compared to that in the control group (*42*). In a study by Wang *et al*., low-frequency US irradiation slightly decreased the migration of pancreatic cancer cells (*40*). When cells have stem cell-like features, they were considered to be the main cause of metastasis and drug resistance (*43*). Yang *et al*. found that low-intensity US suppressed the migration of ovarian cancer stem cells by inducing morphological changes, F-actin formation, and increasing membrane stiffness (*44*). These findings indicate that under appropriate conditions, low-frequency US irradiation will not damage the skin of the experimental subject or even the patient, its effect on cancer cells and normal cells differs significantly, and it inhibits the metastasis of cancer cells to a certain degree.

There were several limitations in this study. First, this study was based on a single type of breast cancer cell, whereas there are multiple types of breast cancer cells in clinical practice. More experiments need to be designed to verify whether low-frequency US combined with MBs will still work on the other types of breast cancer. Second, this study did not explore underlying mechanisms. The continued exploration of cavitation, its molecular mechanisms, and the dose-response relationship between US parameters and anticancer efficiency need to be further studied. Third, this study only noted an inhibitory effect of low-frequency US irradiation on breast cancer cells, but the treatment failed to completely destroy cancer cells, so whether it can be used alone in clinical settings or how it can be combined with other treatments, such as chemotherapy and radiotherapy, needs to be verified further.

In conclusion, the results of this study indicated that combining low-frequency US with MBs can suppress tumor growth by inducing apoptosis and blocking the blood supply. The optimization of low-frequency US treatment should enable it to be an essential tool in the treatment of breast cancer.

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

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BRIEF REPORT
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Evaluation of X-ray protective goggles in mitigating eye lens radiation exposure during radiopharmaceutical handling and patient care in nuclear medicine

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Abstract: The aim of this study is to estimate eye lens exposure dose when handling radiopharmaceuticals and interacting with patients receiving radiopharmaceuticals, and to verify the usefulness of X-ray protective goggles in mitigating such radiation exposure using phantoms. To evaluate radiation exposure during the handling of radiopharmaceuticals, we employed a fluorescent glass dosimeter to measure the radiation doses associated with ^{99m}Tc, ^{123}I, ^{131}I, ^{111}In, and ^{18}F at distances of 30 cm and 60 cm, followed by calculation of the 3 mm dose equivalent rate (3DER). We then estimated the dose reduction rates for various scenarios, including the use of syringe shields and X-ray protective goggles with lead equivalences of 0.07, 0.15, 0.75, and 0.88 mmPb, as well as their combined application. X-ray protective goggles with lead equivalence of 0.75 mmPb outperformed those with 0.07 mmPb and 0.15 mmPb, for all radionuclides and at both source distances. X-ray protective goggles with 0.88 mmPb outperformed those with 0.75 mmPb during handling of ^{131}I and ^{111}In at a distance of 30 cm. In the remaining scenarios, X-ray protective goggles with 0.88 mmPb resulted in marginal reductions or no discernible additional effects. The overall shielding effect of X-ray protective goggles was less pronounced for ^{131}I and ^{18}F, but the combined use of a syringe shield with X-ray protective goggles with 0.75 or 0.88 mmPb improved the dose reduction rate for all scenarios. In simulating patient care, X-ray protective goggles with 0.88 mmPb demonstrated a dose reduction effect of approximately 50% or more. X-ray protective goggles could reduce the 3DER for the eye lens, and were more effective when combined with a syringe shield. It is valid to use a lead equivalence of 0.88 mmPb to fully harness the protective capabilities of X-ray shielding goggles when dealing with all five types of nuclides in clinical settings.

Keywords: X-ray protective goggles, eye lens protection, radiation shielding, single photon emission computed tomography (SPECT), positron emission tomography (PET)

Introduction

Prior to 2011, the accepted threshold dose for radiation induced cataracts was set as 1.5 Gy, but several studies have suggested that cataracts could develop with radiation exposure of less than this (*1-5*). In response to this evidence, the International Commission on Radiological Protection (ICRP) issued a statement on tissue reactions to radiation exposure (Seoul Statement) in April 2011, lowering the threshold radiation dose for potential cataracts to 0.5 Gy. Furthermore, the limit of the equivalent dose to the eye lens of radiation workers was changed to "20 mSv on average for five years and not to exceed 50 mSv in any one year" from that previously set as "not to exceed 150 mSv per year" (*6,7*). The Ordinance on Prevention of Ionizing Radiation Hazards in Japan was revised to align with the threshold set by the ICRP, which was effective from April 1, 2021.

Regarding X-ray examinations, X-ray protective glasses have been recommended for cardiac interventional radiology (IVR) based on reports that 0.07 mmPb X-ray protective glasses enable a reduction in eye lens exposure of approximately 60% (*8,9*). In nuclear medicine examinations, the use of syringe shields, lead-containing protective plates, and X-ray protective glasses have been shown to reduce radiation exposure of eye lens (*10-12*). Matsutomo *et al*. reported that the use of 0.75 mmPb X-ray protective goggles when handling radiopharmaceuticals resulted in a

significant radiation dose reduction of 68.8% for ^{99m}Tc, 60.6% for ^{111}In, and 68.1% for ^{123}I (*12*). However, there have been no reports examining the usefulness of X-ray protective goggles when it is necessary to be near a patient lying in bed during a nuclear medicine examination, such as when the patient's condition requires assistance.

The aim of this study was to estimate the 3 mm dose equivalent rate (3DER) for the eye lens and the usefulness of X-ray protective goggles when handling radiopharmaceuticals with five nuclides, ^{99m}Tc, ^{123}I, ^{131}I, ^{111}In, and ^{18}F. In addition, for the two major nuclides ^{18}F and ^{99m}Tc, we estimated the 3DER when interacting with patients receiving radiopharmaceuticals, and assessed the utility of X-ray protective goggles for mitigating exposure of eye lens to radiation.

The standard method for managing the equivalent dose to the eye lens is to use 1cm dose equivalent, 3 mm dose equivalent, and 70 μm dose equivalent, depending on the type and energy of radiation. However, because a glass dosimeter was used in this study, the 3 mm dose equivalent rate was calculated by measuring air kerma. This verification was conducted using phantoms.

Materials and Methods

Dose measurements were performed using a fluorescent glass dosimeter/small element system (Dose Ace FGD-1000; ACG TECHNO GLASS Co., Ltd. Shizuoka, Japan). Dosimetry was performed using a radiophotoluminescent glass dosimeter (RPLD) attached to the eyeball of a CT head phantom. Types of RPLD were GD-352M for the assessment of ^{99m}Tc, and GD-302M for the assessment of ^{18}F, ^{131}I, ^{111}In, and 123I. We read an initial value of air kerma for each fluorescent glass dosimeter. After irradiation (measurement) while in the holder, preheating was performed at 70 oC for 30 minutes, and the measured values were read after being left at room temperature until the temperature dropped to below 30 oC (13). Regarding syringe shields, a UG-WS-25 shield (UNIVERSAL GIKEN, Kanagawa, Japan) was used for SPECT preparations and a UG-FWS-TR50 tungsten shield (UNIVERSAL GIKEN) was used for 18F preparations. We used a NEMA IEC body phantom to verify measurements when interacting with patients. Four types of X-ray protective goggles were used: 0.07 mmPb Panorama Shield (TORAY MEDICAL, Tokyo, Japan), 0.15 mmPb EC-10 XRAY (ERICA OPTICAL, Fukui, Japan), 0.75 mmPb X-Guard Click Monarch (SHOWA OPT, Osaka, Japan), and 0.88 mmPb Dr. B-Go (Dr. Japan, Tokyo, Japan) (Figure 1).

Verification of radiation dose

The nuclides assessed in this study were selected based on the results of a survey that included the frequency of use of nuclides in nuclear medicine in Japan, which appear to be generally consistent with those in use worldwide (*14*). Radiation measurements were conducted for sealed syringes containing 260 MBq of ^{99m}Tc, 50 MBq of ^{111}In, 158 MBq of ^{123}I, 36.5 MBq of ^{131}I, and 240 MBq of ^{18}F, and these doses were set to simulate their use in a clinical scenario.

In the assessment of simulated patient care during a nuclear medicine examination, the background concentrations of the phantom were 18.0 kBq/ml for ^{99m}Tc and 2.65 kBq/ml for ^{18}F, following accepted guidelines for phantom testing (*15,16*).

Estimation of 3 mm dose equivalent

In this study, air kerma read were taken five times and the average value was used. To estimate the

Index	Panorama Shield (TORAY MEDICAL)	EC-10 XRAY (ERICA OPTICAL)	X-Guard Click Monarch (SHOWA OPT)	Dr.B-Go (Dr.Japan)
Lead equivalent (mmPb)	0.07	0.15	0.75	0.88
Weight (g)	65	69	85	100
Combined use with vision correction glasses	○	○	X	X

Figure 1. Characteristics of X-ray protective goggles.

exposure of eye lens to radiation when handling radiopharmaceuticals and simulated patient care, we calculated the 3DER by the formula (A) as follows:

$$E = \frac{k}{0.9} \times D \times \frac{\frac{\lambda}{1-e^{-\lambda t}}}{B} \quad \cdots\cdots (A)$$

E: 3 mm dose equivalent rate per radioactivity (μSv/min/GBq)

D: air kerma (μGy)

λ: decay constant (/min)

B: radioactivity amount at start of measurement (GBq)

t: measurement time (min)

k: conversion factor from air kerma to 3 mm dose equivalent (Sv/Gy)

The mutual response value of RPLD to the energy of the radionuclide was fixed to 0.9 (*12,13*). The conversion coefficient from air kerma to 3 mm dose equivalent (*k*) was 1.449 for ^{99m}Tc and ^{123}I, 1.286 for ^{131}I, 1.372 for ^{111}In, and 1.210 for ^{18}F (*12,17*).

Verification when handling radiopharmaceuticals

The distance between the eye lens and the radioactive material was set at 60 cm based on the average length of the arm in Japanese individuals. A setting of 30 cm was also used, to allow for bending of the elbows during work (*12*). Radiation measurements were conducted continuously for 1 hour for the following four situations: *i*) with no protection, *ii*) using only the syringe shield, *iii*) using only the X-ray protective goggles, and *iv*) using both the syringe shield and the protective goggles.

Simulated patient care

In the simulation of patient care during a nuclear medicine examination, measurements were obtained at distances of 30 and 60 cm, and the height of the bed was set at 95 cm. Measurements were made with the eyeball of the brain phantom set at heights of either 150 and 165 cm from the floor, consistent with the average heights of Japanese women and men, respectively (Figure 2). Radiation dose measurements were conducted continuously for 30 minutes, and the 3DER was calculated for these specific conditions.

Results and Discussion

In this study, we estimated the 3DER for the eye lens and the usefulness of X-ray protective goggles when handling radiopharmaceuticals prepared with each of five nuclides (^{99m}Tc, ^{123}I, ^{131}I, ^{111}In, ^{18}F). For the two major nuclides, ^{18}F and ^{99m}Tc, we also estimated 3DER when interacting with patients receiving radiopharmaceuticals and assessed the utility of X-ray protective goggles.

Shielding effect of syringe shield when handling radiopharmaceuticals

Table 1 summarizes the shielding effect of the syringe shield for each radionuclide at radioactive source distances of 30 and 60 cm. The syringe shield reduced the 3DER of ^{99m}Tc, ^{123}I, ^{111}In, and ^{18}F by more than 70%, and reduced the 3DER of ^{131}I by about 30%. Except for ^{18}F, the reduction in 3DER was more pronounced at a distance of 60 cm than at 30 cm.

In simulation of bone scintigraphy (^{99m}Tc, 950 MBq) and PET examination (^{18}F, 240 MBq), if radiopharmaceuticals are handled for 5 minutes a day at a distance of 30 cm and without radiation protection, the annual eye lens equivalent dose (240 days) is estimated as 5.94 mSv/year for ^{99m}Tc and 8.63 mSv/year for ^{18}F, based on the results of the 3DER.

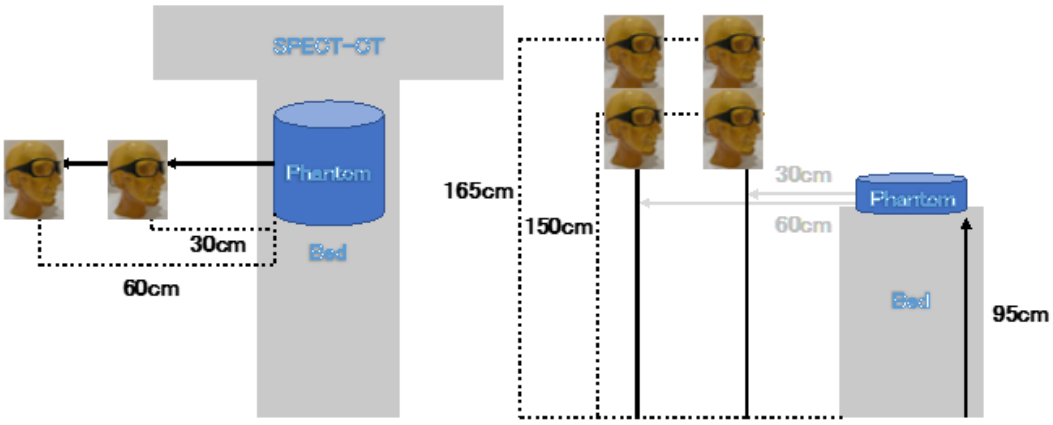

Figure 2. Phantom installation diagram (Horizontal/vertical direction).

Table 1. Comparison of 3mm dose equivalent rate with and without syringe shield at distance of 30 cm and 60 cm

Radionuclide	Protection	Distance of 30 cm		Distance of 60 cm	
		3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)	3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)
^{99m}Tc	None	5.21 ± 0.06	-	5.21 ± 0.06	-
	Syringe shield	0.93 ± 0.00	82.1	0.93 ± 0.00	82.1
^{123}I	None	8.94 ± 0.31	-	8.94 ± 0.31	-
	Syringe shield	2.58 ± 0.08	71.1	2.58 ± 0.08	71.1
^{131}I	None	16.70 ± 1.35	-	16.70 ± 1.35	-
	Syringe shield	11.88 ± 0.55	28.9	11.88 ± 0.55	28.9
^{111}In	None	25.71 ± 0.68	-	25.71 ± 0.68	-
	Syringe shield	8.13 ± 0.36	68.4	8.13 ± 0.36	68.4
^{18}F	None	29.97 ± 0.19	-	29.97 ± 0.19	-
	Syringe shield	4.85 ± 0.08	83.8	4.85 ± 0.08	83.8

Table 2. Reduction of 3 mm dose equivalent rate by X-ray protective goggles (distance-dependent variations)

Radionuclide	Goggle for protection	Distance of 30 cm		Distance of 60 cm	
		3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)	3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)
^{99m}Tc	None	5.21 ± 0.06	-	1.63 ± 0.05	-
	0.07 mmPb	3.62 ± 0.07	30.6	1.28 ± 0.09	21.5
	0.15 mmPb	3.39 ± 0.05	34.9	1.10 ± 0.12	32.9
	0.75 mmPb	0.83 ± 0.10	84.1	0.39 ± 0.05	76.0
	0.88 mmPb	0.89 ± 0.06	82.9	0.43 ± 0.05	73.4
^{123}I	None	8.94 ± 0.31	-	6.15 ± 0.08	-
	0.07 mmPb	5.00 ± 0.09	44.1	2.11 ± 0.37	65.8
	0.15 mmPb	4.53 ± 0.19	51.3	2.24 ± 0.14	63.5
	0.75 mmPb	2.58 ± 0.14	71.1	0.78 ± 0.09	87.3
	0.88 mmPb	2.75 ± 0.19	69.2	0.65 ± 0.08	89.5
^{131}I	None	16.70 ± 1.35	-	8.61 ± 0.29	-
	0.07 mmPb	15.53 ± 0.85	7.0	6.66 ± 0.55	22.7
	0.15 mmPb	14.35 ± 0.80	14.1	5.22 ± 0.00	39.4
	0.75 mmPb	12.27 ± 0.71	26.6	4.70 ± 0.71	45.5
	0.88 mmPb	10.31 ± 0.29	38.3	6.00 ± 1.26	30.3
^{111}In	None	25.71 ± 0.68	-	13.92 ± 0.58	-
	0.07 mmPb	13.52 ± 0.45	47.4	7.93 ± 0.28	43.1
	0.15 mmPb	13.42 ± 0.28	47.8	5.29 ± 0.28	62.0
	0.75 mmPb	10.57 ± 0.43	58.9	3.86 ± 0.28	72.3
	0.88 mmPb	7.62 ± 0.36	70.4	3.46 ± 0.43	75.2
^{18}F	None	29.97 ± 0.19	-	8.34 ± 0.11	-
	0.07 mmPb	26.96 ± 0.10	10.1	8.00 ± 0.19	4.0
	0.15 mmPb	26.62 ± 0.22	11.2	7.10 ± 0.08	14.8
	0.75 mmPb	22.82 ± 0.05	23.9	6.84 ± 0.07	18.0
	0.88 mmPb	21.90 ± 0.10	26.9	6.82 ± 0.04	18.2

Shielding effect of X-ray protective goggles when handling radiopharmaceuticals

Table 2 summarizes the shielding effect of X-ray protective goggles for each radionuclide at radioactive source distances of 30 and 60 cm.

X-ray protective goggles with lead equivalence of 0.75 mmPb outperformed those with 0.07 mmPb and 0.15 mmPb, for all radionuclides and at both source distances. X-ray protective goggles with 0.88 mmPb outperformed those with 0.75 mmPb during handling of ^{131}I and ^{111}In at a distance of 30 cm. However, in the remaining scenarios, X-ray protective goggles with lead equivalence of 0.88 mmPb resulted in only marginal reductions or no discernible additional effects. The overall shielding effect of X-ray protective goggles was less pronounced for ^{131}I and ^{18}F in comparison with the other radionuclides.

All of the tested X-ray protective goggles demonstrated a dose reduction effect, and the dose reduction rate tended to improve as the lead equivalence increased. In particular, by using 0.88 mmPb X-ray protective goggles, a high dose reduction effect of approximately 70% or more was obtained for ^{99m}Tc, ^{123}I, and ^{111}In, and the reduction rate was about 20% to 40% for ^{131}I and ^{18}F.

Although it has been reported that syringe shields alone are effective in reducing radiation exposure

Table 3. Reduction of 3 mm dose equivalent rate by X-ray protective goggles with syringe shield (distance-dependent variations)

Radionuclide	Goggles combined with a syringe shield	Distance of 30 cm			Distance of 60 cm		
		3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)	Reduction (%) by goggle	3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)	Reduction (%) by goggle
^{99m}Tc	Syringe shield only	0.93 ± 0.00	82.1	-	0.27 ± 0.06	83.5	-
	0.07 mmPb	0.79 ± 0.06	84.9	15.6	0.10 ± 0.00	93.7	61.5
	0.15 mmPb	0.79 ± 0.09	84.9	15.6	0.31 ± 0.07	81.0	-15.4
	0.75 mmPb	0.52 ± 0.07	90.1	44.4	0.31 ± 0.10	81.0	-15.4
	0.88 mmPb	0.31 ± 0.00	94.1	66.7	0.21 ± 0.10	87.3	87.3
^{123}I	Syringe shield only	2.58 ± 0.08	71.1	-	0.78 ± 0.09	87.3	-
	0.07 mmPb	1.19 ± 0.12	86.7	54.0	0.48 ± 0.14	92.3	52.4
	0.15 mmPb	0.68 ± 0.00	92.4	73.7	1.02 ± 0.12	83.4	28.7
	0.75 mmPb	0.71 ± 0.14	92.0	72.4	0.71 ± 0.14	88.4	33.3
	0.88 mmPb	0.95 ± 0.19	89.4	63.2	1.22 ± 0.08	80.1	19.1
^{131}I	Syringe shield only	11.88 ± 0.55	28.9	-	5.35 ± 0.71	37.9	-
	0.07 mmPb	8.87 ± 0.58	46.9	25.3	4.83 ± 0.36	43.9	9.8
	0.15 mmPb	10.96 ± 0.55	34.4	7.7	4.96 ± 0.36	42.4	7.3
	0.75 mmPb	6.52 ± 0.46	60.9	45.1	2.48 ± 1.26	71.2	53.7
	0.88 mmPb	5.74 ± 0.55	65.6	51.7	2.87 ± 0.74	66.7	46.3
^{111}In	Syringe shield only	8.13 ± 0.36	68.4	-	4.17 ± 0.56	70.1	-
	0.07 mmPb	4.07 ± 0.62	84.2	50.0	2.44 ± 0.43	82.5	41.5
	0.15 mmPb	2.95 ± 0.43	88.5	88.5	2.74 ± 0.58	80.3	34.2
	0.75 mmPb	5.49 ± 0.43	78.7	78.7	2.95 ± 0.43	78.9	29.3
	0.88 mmPb	2.34 ± 0.85	90.9	90.9	2.95 ± 0.23	78.8	29.3
^{18}F	Syringe shield only	4.85 ± 0.08	83.8	-	1.87 ± 0.07	77.5	-
	0.07 mmPb	4.66 ± 0.08	84.4	3.9	1.54 ± 0.11	81.6	18.0
	0.15 mmPb	4.61 ± 0.04	84.6	5.0	1.67 ± 0.10	80.0	11.0
	0.75 mmPb	3.03 ± 0.05	89.9	37.5	1.09 ± 0.05	87.0	42.0
	0.88 mmPb	3.45 ± 0.08	88.5	29.0	1.09 ± 0.08	87.0	42.0

(*10*), wearing X-ray protective goggles may provide an additional reduction in the exposure of eye lens to radiation, especially in cases of difficulties such as mismatches between syringe and syringe shields.

Shielding effect of combined syringe shield with X-ray protective goggles when handling radiopharmaceuticals

Table 3 shows the results of measurements performed using both a syringe shield and goggles. "Reduction [%] by goggle" in Table 3 is the percentage difference in the 3DER between using only a syringe shield and using both a syringe shield and goggles. At both distances, radiation dose tended to decrease as the lead equivalence of the X-ray protective goggles increased, particularly for ^{131}I and ^{111}In. Dose reduction depended largely on the use of a syringe shield and the source distance for ^{99m}Tc, and on the use of a syringe shield for ^{123}I. When a syringe shield and X-ray protective goggles were both used at a distance of 30 cm from the source, improvements in dose reduction rate were observed for all nuclides. Based on these results, it is considered beneficial to wear X-ray protective goggles in addition to using a syringe shield when the radiation worker should stay close to the radiation source and handle radionuclides with high energy and a long half-life.

In terms of effects on the 3DER and the reduction rate, it is imperative to use X-ray protective goggles with a minimum 0.75 mmPb to fully harness the protective capabilities of it when dealing with all five types of nuclides in clinical settings.

The dose reduction rate achieved using a syringe shield or X-ray protective goggles was lower for ^{131}I than for other nuclides. The reason for this finding appears to be that ^{131}I has an energy of 364 keV and a half-life of about 8 days, which are both higher values than for other nuclides. However, the present results indicate that combined use of a syringe shield with X-ray protective goggles would contribute to improving the dose reduction rate for ^{131}I.

When handling ^{18}F radiopharmaceuticals, the 3DER can be reduced from 8.63 mSv/year to 1.40 mSv/year by using a syringe shield, and that further reductions can be achieved by the combined use of a syringe shield with X-ray protective goggles.

Verification of shielding effect of X-ray protective goggles in simulated patient care

Table 4 shows the results of the shielding effect of X-ray protective goggles for two radionuclides (^{99m}Tc and^{18}F) at distances of 30 and 60 cm from the NEMA phantom. At all distances and heights, the dose reduction rate improved as lead equivalence increased. The results of the NEMA phantom study indicated that X-ray protective goggles with 0.88 mmPb are

Table 4. Reduction of 3 mm dose equivalent rate by X-ray protective goggles based on NEMA phantom study (distance-dependent variations)

Radionuclide	Height (cm)	Goggle for protection	Distance of 30 cm		Distance of 60 cm	
			3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)	3 mm dose equivalent rate (μSv/min/GBq)	Reduction (%)
^{99m}Tc	150	None	1.45 ± 0.20	-	1.16 ± 0.35	-
		0.07 mmPb	1.45 ± 0.35	0.0	1.13 ± 0.29	2.5
		0.15 mmPb	1.16 ± 0.20	20.0	0.87 ± 0.29	25.0
		0.75 mmPb	0.87 ± 0.20	40.0	0.58 ± 0.20	50.0
		0.88 mmPb	0.58 ± 0.35	60.0	0.46 ± 0.22	60.0
	165	None	1.04 ± 0.33	-	1.04 ± 0.30	-
		0.07 mmPb	0.87 ± 0.25	16.7	1.04 ± 0.38	0.0
		0.15 mmPb	0.69 ± 0.34	33.9	0.97 ± 0.30	6.9
		0.75 mmPb	0.52 ± 0.48	50.0	0.52 ± 0.40	50.0
		0.88 mmPb	0.52 ± 0.31	50.0	0.52 ± 0.56	50.0
^{18}F	150	None	18.09 ± 1.64	-	14.80 ± 2.01	-
		0.07 mmPb	18.09 ± 0.00	0.0	13.16 ± 2.01	11.1
		0.15 mmPb	16.44 ± 1.64	9.1	11.51 ± 1.64	22.2
		0.75 mmPb	9.87 ± 5.07	45.5	8.22 ± 1.64	44.4
		0.88 mmPb	9.87 ± 1.16	45.5	4.93 ± 2.60	66.7
	165	None	13.81 ± 3.00	-	13.32 ± 1.90	-
		0.07 mmPb	12.83 ± 6.64	7.1	13.32 ± 1.43	0.0
		0.15 mmPb	11.84 ± 1.96	14.3	10.36 ± 1.12	22.2
		0.75 mmPb	9.87 ± 3.08	28.6	7.40 ± 2.32	44.4
		0.88 mmPb	6.91 ± 1.57	50.0	5.92 ± 2.43	55.6

optimal for achieving maximum dose reduction under all circumstances. Even at a source distance of 60 cm, the present results demonstrated the efficacy of X-ray protective goggles for reducing radiation dose, and that this effect was more prominent when using X-ray protective goggles with 0.88 mmPb equivalence.

The use of X-ray protective goggles of 0.75 mmPb equivalence reduced radiation dose for various radiation sources, as found in the assessment of dose to the eyeball in a CT head phantom (Table 2). However, the 0.88 mmPb X-ray protective goggles reduced the dose by more than 50%, which was greater than that with the 0.75 mm X-ray protective goggles in the assessment performed using the NEMA phantom to simulate patient care. Considering the difference between the radiation source and the NEMA phantom, 0.88 mmPb X-ray protective goggles might be the most effective for reducing radiation coming from a wider range of sources.

With reference to background radiation dose in the phantom studies according to the Imaging Guidelines for Phantom Studies (*15,16*), in simulation of the situation of attending to each patient for 10 minutes, for 10 people per day, the estimated radiation exposure received from patients was 6.44 mSv/year for ^{99m}Tc and 11.85 mSv/year for ^{18}F. Under this condition, when exposure during handling of radiopharmaceuticals is also taken into account, the average value over a five-year period could exceed the dose limit for ^{18}F. In simulation of patient care of PET examination, the 3DER can be reduced from 11.85 mSv/year to 6.46 mSv/year by using 0.88 mmPb X-ray protective goggles. In the case of the other nuclides, using this equipment will also contribute to minimizing the 3DER.

The results showed that X-ray protective goggles could reduce the 3DER for the eye lens, and were most effective when combined with a syringe shield. However, it is imperative to use a syringe shield with a minimum equivalence of 0.88 mmPb to fully harness the protective capabilities of X-ray shielding goggles when dealing with all five types of nuclides in clinical settings. Matsutomo *et al.* reported that for X-ray protective goggles, lead equivalence of around 0.75 mmPb or higher is desirable when handling radiopharmaceuticals (*12*), in agreement with the present results. Our study additionally assessed a greater variety of nuclides and conducted a simulation of patient care. However, it is important to note that as the lead equivalence increases, the increasing weight of the goggles and narrowing of the field of view may become burdensome for the wearer, particularly when worn for a long period of time. Moreover, some protective goggles cannot be used while wearing corrective eyeglasses. In addition, lutetium oxodotreotide (^{177}Lu), which has recently been used in Japan as a nuclear medicine treatment for neuroendocrine tumors, has a very high dose of 7.4 GBq per dose, so it is expected that crystalline lens protection glasses specialized for nuclear medicine examinations will be developed in the future.

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Strengthening health systems during non-pandemic period: Toward universal health coverage in the pandemic agreement

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Abstract: Reflecting the experiences of the COVID-19 pandemic, the global response was reviewed by the Independent Review Panel for Pandemic Preparedness and Response. Based on the panel reports, the World Health Organization (WHO) member states decided to establish the intergovernmental negotiating body for drafting a WHO convention, agreement or other international instrument on pandemic prevention, preparedness and response, aiming for approval at the 77th World Health Assembly in 2024 (May 27- June 1). Amidst this process, the National Center for Global Health and Medicine, Japan (NCGM), as a global health organization focusing on health system strengthening in low- and middle-income countries, from the perspective of Universal Health Coverage (UHC), provided technical inputs to the representatives of the Japanese government. This paper summarizes crucial aspects of the NCGM inputs, including maintaining essential health services delivery during a pandemic, responding to evolving demand of health workforce, and ensuring the equitable distribution of pandemic products. These aspects can contribute to not only strengthening health crisis response and preparedness, but also achieving UHC. Therefore, the concerted efforts focusing on UHC and health crisis could yield synergistic effects. In addition, another aspect stresses the importance of social protection systems beyond health sector to reach vulnerable populations experiencing hardships during the COVID-19 pandemic. Since the whole-of-government approach including social policies is covered in the draft pandemic agreement, it is hoped that the upcoming pandemic agreement will trigger each member state to expand the scope of health crisis management beyond the health sector.

***Keywords*:** pandemic agreement, UHC, IHR, Health Security

Introduction

Since the first COVID-19 case was reported in China in December 2019 (*1*), SARS-CoV-2 rapidly spread around the world, leading to a declaration of "pandemic" by the World Health Organization (WHO) Director-General in March 2020 (*2*). Subsequently, continuous spread of the virus caused significant socio-economic losses and impacted non-COVID-19 health services worldwide.

Responding to the resolution of 73rd World Health Assembly (WHA) held in 2020, the independent panel for pandemic preparedness and response (IPPPR) was organized to review the WHO's response (*3*). Six months later, the IPPPR compiled the reports (*4*) during the 2nd Special WHA in December 2021, leading to the decision to establish the inter-governmental negotiation body (INB) to draft and negotiate a WHO convention, agreement or other international instrument on pandemic prevention, preparedness and response, aimed for approval at the 77th WHA in May 2024 (*5*). Subsequent intermittent meetings of INB organized the discussions on the agreement draft, culminating in the submission of the Negotiating Text in October 2023 (*6*), followed by the Revised Negotiating Text in March 2024 (*7*). Then, the outcome of INB including texts still under negotiations was submitted to the 77th WHA (*8*) for further consideration as a legally binding policy document covering comprehensively a wide range of items (*e.g.* strengthening health systems, manufacturing and access to related medical products, fundraising, and societal efforts beyond health), which after all, was agreed to extend the negotiation period for up to one year.

Throughout this process, we, the Bureau of International Health Cooperation, the National Center for Global Health and Medicine, Japan (NCGM), as a global health organization focusing on health system strengthening in low- and middle-income countries (LMICs) with the aim of Universal Health Coverage (UHC) achievement, have provided technical inputs to

Table 1. Crucial aspects of health system strengthening to be addressed from perspective of UHC in preparation for future pandemic and related article of negotiating text at 77th WHA

Addressing the "resilience" of health systems to the challenges clarified after the pandemic	
• Strengthening service delivery that does not cease even during a pandemic by – Developing the service continuity plans during pandemic and the simulations, – Strengthening health information system to capture health resources and utilization of those, – Leveraging lessons learned from previous pandemic and other emergency events, including community system or digital health.	Article 6
• Responding to evolving demand of healthcare workforce by – Providing opportunities to learn the basics of pandemic response and preparation, – Maintaining a surplus of workforce capacity during non-pandemic period to handle the pandemic response, – Building the capacity for community engagement, aligning with Primary Health Care oriented system.	Article 7
• Enhancing the domestic logistics for equitable distribution of pandemic products by – Assessing the capability of domestic supply chains, including the cold-chain system, regularly for further strengthening of the absorption capacity, – Considering the reduction of medical waste and the cost burden of waste disposal.	Article 13
Establishment of social protection system beyond the health sector to protect people's livelihoods even in times of city lockdowns and other social countermeasures	
• Strengthening resident registration system such as Civil Registration and Vital Statistics, national ID, • Having mechanisms and legal frameworks for social assistance as part of routine surge financing for health crises, • Enhancing coordinating mechanisms involving stakeholders across sectors during pandemic.	Article 17

the representatives of Japanese government participating in INB meetings, drawing on our longstanding experience and accumulated knowledge (*9*). Based on these experiences, at the time of the 77th WHA in 2024 (May 27- June 1), we summarized here crucial aspects of health system strengthening in preparation for future pandemics which are to be addressed particularly in LMICs from the perspective of UHC (Table 1).

Addressing the "resilience" of health systems to the challenges clarified after the pandemic

Strengthening service delivery that does not cease even during a pandemic

The experience of COVID-19 pandemic highlighted the importance of ensuring uninterrupted essential health services during health crises. In fact, during the pandemic, routine immunization programs have been delayed in many countries, leading to outbreaks of vaccine-preventable diseases (*10*). Considering these points, while the negotiating texts at the 77th WHA includes provisions regarding the maintenance of health services in Article 6, it does not mention the specific strategies. Such strategies are shown as follows.

First, development of emergency response plans during the non-pandemic period including service continuity plan should be highlighted to ensure uninterrupted essential health service delivery even during a pandemic. Based on the plans, regular simulations and training exercises should be also considered to provide more concrete knowledge and skills for the participants. Regarding the measures of the plan, there is potential to leverage lessons learned from efforts in response not only to pandemics but also to natural disasters, extreme weather conditions, and geographically isolated islands, which may be related to climate change. The applicable interventions may include multi-dose prescriptions for chronic diseases, mobilizing community systems through collaboration with civil society organization (CSO) / community based organization (CBO), and clinical monitoring via digital platforms.

Second, strengthening health information systems, including health information not directly related to pandemic diseases but to health resources, is crucial to maintain effective health service delivery as well as to monitor epidemic situations and intervention results. Information about resources such as health workforce, health facilities including equipment, and pharmaceuticals, utilization of those and the quality of services should be helpful to efficiently and effectively distribute limited resources to areas with high potential demand. Information, such as high-care unit bed occupancy, will also be important for triangulation of epidemiological information in the early stages of a pandemic when disease definition is not clear.

Some existing global guidance, for instance, in the field of human resources for health workforce cover the activities to maintain essential health services during health crises, including monitoring and evaluation of the implementation status (*11*). It is hoped that WHO will leverage these relevant documents to support each member state to implement the pandemic agreement.

Responding to evolving demand of health workforce

While Article 7 already addresses this issue, it is important to reiterate the significance of the healthcare workforce. The pandemic has highlighted quantitative and qualitative shortages of health workforce, regional and occupational disparities in distribution and retention, constrained labor markets, and vulnerable pre- and in-service training systems (*12*). Wide ranges of health workforce challenges have already been analyzed since the pre-pandemic period. Nonetheless, health workforce attrition and shortages would continue over the post-pandemic period and could destabilize the health system itself. Without solid and effective measures, preparedness and response to any future health crisis would be impossible (*13-15*).

What is needed for the health workforce to respond to crisis are: *i*) providing all health workforce with opportunities to learn the basics of pandemic response and preparation such as surveillance, early detection of diseases, infection prevention and control (IPC), through incorporation into pre- and in-service training during the non-pandemic period, and *ii*) maintaining a surplus of workforce capacity during the non-pandemic period even when it overlaps with regular duties, to ensure resilience to handle the pandemic response. Aligning health workforce policies with the Primary Health Care (PHC) oriented system (*13*) is particularly essential to provide necessary health care to the vulnerable or the hard-to-reach population to achieve UHC, even during the health crisis. Such a policy example is to invest in multidisciplinary PHC teams with optimized skill mix, adjusted scope of practice, and support with digital technologies, as well as enhanced collaboration with CSO/CBO to gain community engagement. Such PHC oriented systems can also contribute to early detection and risk assessment during a future pandemic.

At both national and local levels, capacity-building for health work force, including community engagement, becomes particularly important. Since the activities by government could not cover both responding to heath crisis and ensuring essential healthcare services at the same time, collaboration with community through CSO/CBO should be emphasized as surge capacity to increase the likelihood of necessary service delivery to unreached populations. It should be important to collaborate with communities and strengthen their capacities during a non-pandemic period.

Equitable distribution of pandemic products

While the negotiating texts of pandemic agreement at the 77th WHA emphasized the various items related to the equitable distribution of pharmaceuticals, particularly "pandemic products", during health crises, such as technology transfer, diversified manufacturing on a regional basis, global supply chain networks, and rules for international allocation, we would like to emphasize more on the importance of domestic supply chains in each country. The ability of regular medical supplies will, of course, greatly affect the ability to supply pandemic products in an emergency. During this pandemic, some of the COVID 19 vaccine required ultra-low temperature storage & transport for vaccines, ultra-cold chain, that posed challenges to supply chain infrastructure development in various countries, particularly countries with challenges in the cold chain of regular vaccines, highlighting the importance of maintaining cold chain logistics during the non-pandemic period. Another example is the absorption capacity of pandemic product, which is often in large volumes. Where supply chains are fragile, large quantities of donated pharmaceuticals might not be kept up by domestic supply, resulting in pharmaceuticals being wasted. Therefore, in addition to strengthening supply chains, it is necessary to thoroughly assess the absorption capacity of recipient countries before distributing aid supplies. While Article 13 mentions these points, it is important to re-emphasize the importance of domestic supply chain development during the non-pandemic period to ensure that essential medical products reach vulnerable populations in need during health crises.

In addition, addressing pharmaceutical medical waste is also essential. While Article 13bis mentions coordinating expiration dates, product usability, and the availability of related auxiliary products between recipient countries and supporting agencies to reduce medical waste, there is still a possibility of generating a certain amount of medical waste during emergencies. In such cases, considering the cost burden of waste disposal on the recipient countries becomes important, thus necessitating consideration of the cost burden of medical waste disposal.

Establishment of social protection systems beyond the health sector

During the COVID-19 pandemic, particularly vulnerable populations experiencing economic and psychological hardships due to measures like lockdowns resulted in low utilization of health services and deterioration of health. This highlighted the importance of broad-ranging measures beyond the health sector. For instance, it is crucial to identify who among the population is most vulnerable during a health crisis and maintain information on them during the non-pandemic period. Systematic understanding data such as residential registration, civil registration and vital statistics (CRVS), national IDs, and poverty status allows for the prioritization of social protection measures for impoverished individuals and households during pandemics. As Article 6 addresses such information systems, it is important to note its significance in response, including investigation of the target populations, implementation and monitoring of measures like vaccination campaigns. Furthermore, in countries where CRVS systems are fragile, it is important

to acknowledge those who may fall through the cracks of national ID systems. Governments should engage non-government actors through social contracting agreements to proactively identify vulnerable populations and ensure that pathways for delivering support are in place.

Additionally, during social measures such as lockdowns, protecting the livelihoods of vulnerable populations becomes crucial for effective healthcare responses during health crises. Social security systems for vulnerable populations are important from the perspective of UHC (*16*). In this pandemic, countries that implemented cash transfers to support vulnerable populations during lockdowns protected their health. Having mechanisms and legal frameworks for social assistance like cash transfers as part of routine surge financing for health crises allows for their utilization during emergencies (*16,17*). While Article 17 mentions such comprehensive social efforts, it is important to also consider social protection systems that function during health crises. Organizations like the ILO, UNICEF, and the World Bank are also working on social protection during health crises (*16*), and active collaboration with the healthcare sector, particularly WHO, is desirable.

Furthermore, coordinating mechanisms involving stakeholders across sectors are crucial. During health crises, various actors beyond the healthcare sector, including government ministries, civil society, other countries' governments, and international organizations, are involved. Understanding the strengths and limitations of each organization's support and effectively deploying resources for pandemic response requires coordination. For instance, establishing inter-sectoral coordination mechanisms like Public Health Emergency Operation Centers or Emergency Medical Team Coordination Cells during disasters involving multiple sectors becomes essential for pandemic response (*18,19*). Handling the complex coordination of different actors during pandemics may necessitate setting up domestic coordination mechanisms and conducting simulations and training during the non-pandemic period. In this regard, the upcoming pandemic agreement is expected to cover these elements.

Based on the drafts of the WHO convention, agreement and other international instruments on pandemic prevention, preparedness and response (*6-8*), vital points requiring further consideration, which each member state, especially among LMICs with weak health systems, has to address as part of their preparedness for future pandemics have been summarized. All the aforementioned aspects discuss activities aimed at delivering quality essential healthcare services during the non-pandemic period to all people, including vulnerable groups, and toward achieving UHC, highlight how these activities contribute to effective health crisis management. Furthermore, during the COVID-19 pandemic in Japan, activities such as establishing medical response teams for patients unable to visit hospitals during lockdowns were observed. Such health crisis measures have the potential to enhance a wide range of healthcare services contributing to UHC, including addressing aging and non-communicable diseases. Thus, activities supporting health crisis management and UHC are strongly interrelated, and concerted efforts focusing on both could yield synergistic effects. Expectations are for the pandemic agreement to provide a legal framework for both achieving UHC and advancing global health security together. Additionally, in order to reach vulnerable populations experiencing hardships during a pandemic, this article stressed the importance of not only health system strengthening, but also a social security system beyond the health sector. Since a whole-of-government approach including social policies is covered in the draft pandemic agreement, it is hoped that the upcoming pandemic agreement will trigger each member state to expand the scope of health crisis management beyond the health sector.

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The future of inbound medical care as gauged from the foreigners undergoing complete medical examinations in Japan

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Abstract: Complete medical examinations are a system of preventive medicine unique to Japan. In recent years, Japanese and foreigners have been aware of complete medical examinations. However, the extent to which this concept of comprehensive medical checkup is recognized in different counties is unknown. The National Center for Global Health and Medicine (NCGM) is a facility that has been performing complete medical examinations on inbound visitors since May 2016, and more than 3,500 inbound visitors have been received to date. Based on this track record, the current study analyzed trends in foreigners' demand for medical checkups in Japan. From August 2020 to July 2023, 471 foreign residents in Japan from 22 countries were received. A certain proportion of examinees (approximately 30%) underwent examinations multiple times at a frequency of once a year. In addition, inbound medical visitors resumed starting in January 2023, and 158 inbound examinees were received. Of these, 15.2% of examinees had undergone a complete medical examination at the NCGM before the COVID-19 pandemic. This suggests that inbound medical visitors and foreign residents may regularly undergo complete medical examinations. In order to continue to meet this demand, Japanese medical facilities should enhance their system for receiving such examinees.

Keywords: complete medical examinations, inbound medical care, foreigner, foreign residents

Introduction

Complete medical examinations are a system of preventive medicine unique to Japan that contribute to health maintenance and early detection of diseases (*1*). Moreover, as Japanese people's awareness of health has increased in recent years, demand has increased not only for medical checkups at schools and companies but also for comprehensive checkups that allow for more detailed medical examinations (*2*). That said, inbound visitors underwent medical checkups in Japan (*1*) even before the COVID-19 outbreak (*3*). Japanese medical facilities have also identified a business opportunity, and the number of facilities that have prepared systems to accept those visitors has increased in recent years (*1,4*). However, the extent to which this concept of a complete medical examination is recognized in different countries is unknown.

The National Center for Global Health and Medicine (NCGM) is a medical facility that has been receiving inbound visitors since May 2016, and more than 3,500 inbound visitors have been received to date. Based on this track record, the current study analyzed trends in foreigners' demand for medical checkups in Japan.

Trends in and characteristics of foreigners' demand for medical checkups in Japan: Data from the NCGM

Based on the Japanese Government's inbound tourism policy, the NCGM has been actively receiving many inbound medical visitors since 2016 (*1,5*). However, inbound demand ceased due to the COVID-19 pandemic (*6*). Foreigners mainly from China and Vietnam were already aware of the NCGM, but in response to the pandemic the facility immediately changed its policy to actively receive foreigners living in Japan (*1,5*). By providing free medical interpreting services, a new system was created to meet the needs of foreigners living in Japan who cannot speak Japanese.

As a result, foreign residents in Japan from a total of 22 countries accounted for 471 (5.1%) of 9,299 total medical check-ups from August 2020 to July 2023. The breakdown included 314 Chinese, 66 Koreans, 15 Vietnamese, 12 Americans, 10 British, 9 French, 6 Filipinos, 5 Canadians, 5 Thais, 5 Bangladeshis, 5 Germans, 4 Kenyans, 4 Israelis, 4 Mongolians, 2 Bulgarians, 2 Brazilians, 2 Myanmarese, 1 Swiss, 1 Singaporean, 1 Peruvian, 1 Russian, and 1 Swede. There were 150 people (31.8%) who needed language support,

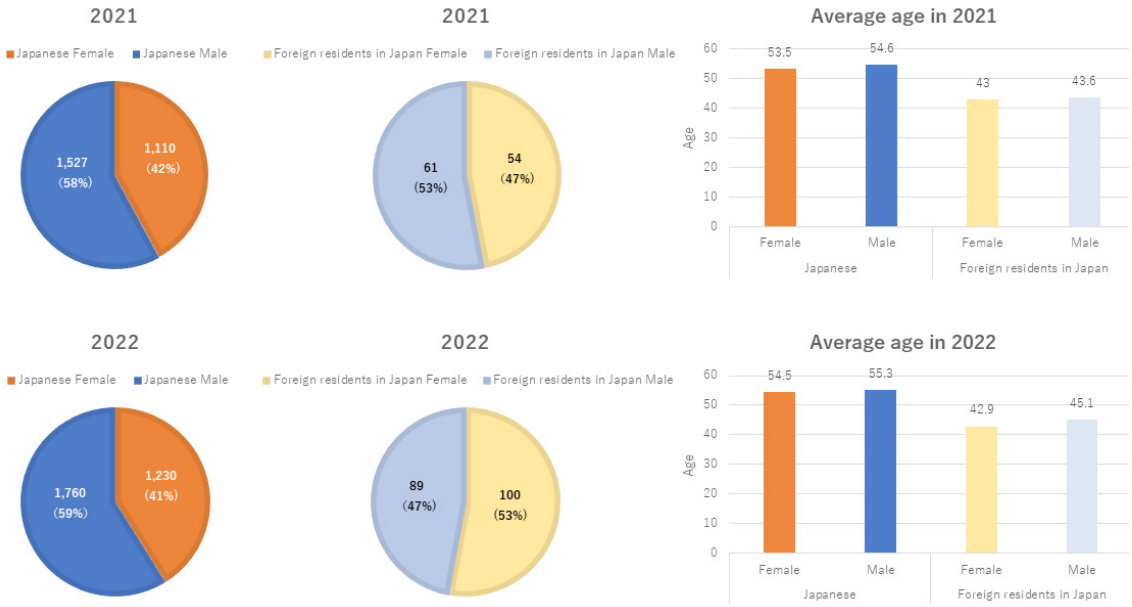

Figure 1. Characteristics of examinees from 2021-2022. Foreign residents in Japan accounted for a higher proportion of female examinees than did Japanese, and the average age of both men and women was about 10 years younger.

and the main languages were Chinese, English, and Vietnamese.

The current study compared data from 2021 and 2022 and analyzed the state of foreign examinees residing in Japan (*5*). Results indicated that the total number of people undergoing a complete medical examination increased 13.8%. In contrast, the number of foreign residents undergoing a complete medical examination increased markedly (64.3%). By country, there was a notable increase in Chinese and Koreans.

The characteristics of foreign residents in Japan were similar to those in 2021, as were previously reported (*5*). In 2022, a higher percentage of foreign residents receiving medical checkups were female compared to Japanese examinees, and the average age of both men and women was about 10 years younger (Figure 1). Moreover, results revealed that a certain number (approximately 30%) of examinees undergo examinations multiple times, and the frequency of such visits is once a year. In Japan, annual checkups such as checkups at schools and companies are compulsory, and this seems to have become a cultural habit. Similarly, the concept of medical checkups, which involves not only single checkups but also regular checkups, is spreading among foreign residents in Japan (Figure 2).

With the end of the COVID-19 pandemic, complete medical examinations for inbound medical visitors resumed at the NCGM starting in January 2023. There were 158 inbound examinees (38.2% Vietnamese, 61.7% Chinese) in total, 24 (15.2%) of whom had previously undergone medical checkups at the NCGM before the COVID-19 outbreak (Figure 2). Accordingly, medical checkups in Japan for inbound medical tourists seem to be more than a fashionable experience and are instead becoming more common as a regular checkup, just like

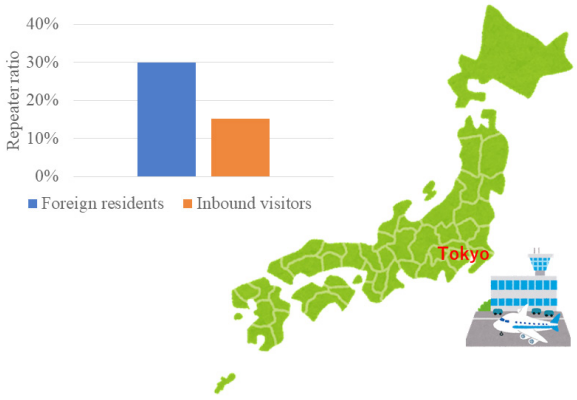

Figure 2. Awareness of medical checkups among foreigners. In recent years, Japanese and foreigners have been aware of complete medical examinations. A certain number of foreigners undergo repeat checkups at the same facility performing complete medical examinations.

for foreigners residing in Japan. Thus, analyzing the trends in medical examinations undergone by foreigners residing in Japan and inbound visitors will help to predict inbound medical tourists undergoing medical checkups on a regular basis, and that information will be extremely useful when considering the state of medical checkups in the future.

The future of inbound medical care as gauged from the foreigners undergoing complete medical examinations in Japan

Based on the current results, awareness of checkups appears to be widespread among both foreign residents and inbound tourists. The average level of medical care in Japan, based on universal health insurance (*7*), is higher than in other countries (*8*), and as long as

this situation continues, demand from foreigners for checkups such as complete medical examinations in Japan will continue to increase. This has the potential to become a major pillar supporting the Japanese economy. New economic benefits are expected not only for those receiving medical care and hospitals but also in various areas including food, clothing, and housing as a result of their arrival in Japan.

In order to continue meeting this demand in the future, the hope is that medical facilities receiving foreigners will enhance their system for doing so. Inbound medical tourists may experience problems during examinations, financial troubles, and various other complaints due to language and cultural differences. As a countermeasure, the NCGM started an innovative medical interpreter registration system in October 2020 to assist inbound visitors. As of July 2023, a total of 103 interviews were conducted, a total of 198 medical interpreters who have passed Level N1 of the Japanese Language Proficiency Test have been registered (*9*), and 84 companies have been certified by the NCGM. This system allows patients to be accompanied by an interpreter with a wealth of medical knowledge who understands hospital rules and Japanese culture through a company that is highly skilled in dealing with inbound tourists. This ensures the quality of interpreting, allows the hospital to receive accurate health information from the patient in a short period of time, and allows the patient to appropriately communicate the purpose of the examination, method of testing, and results. Building such a mutually beneficial relationship should help ensure that checkups satisfy both the examinees and the examiners. Currently, the NCGM has resumed checkups and continues to accept inbound visitors without any trouble, and this system for quality assurance has been effective. Therefore, this seems to be one of the important factors that has allowed the NCGM to grow into one of the most successful facilities performing complete medical examinations for inbound visitors to Japan both before and after the COVID-19 pandemic.

Based on the above achievements and experiences, we would like to point out the problems and points that need to be reformed in Japan's current system of inbound medical care. First, given that the demand for inbound medical care is expected to continue to increase, hospitals currently have difficulty allocating staff to handle inbound visitors. Therefore, the NCGM's system, in which some of these tasks are outsourced to certified companies and medical interpreters and the hospital coordinates them, is one way to accommodate the increasing number of inbound medical tourists. In addition, Japan's inbound medical care is broadly divided into four categories: (A) disease treatment, (B) checkups such as complete medical examinations, (C) cosmetic treatments such as plastic surgery, and (D) life-prolonging care such as stem cell injections and blood purification. In areas such as (D), where there are issues with implementation standards and evidence of effectiveness, if the development is delayed, then (A), (B), and (C) may also be adversely affected. We believe that there is an urgent need for interventions such as management of certification by the department in charge of medical care.

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Understanding the daily life needs of older public assistance recipient subgroups in Japan: A qualitative study

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Abstract: Transition from individual-level treatment to social-level intervention should be made to improve people's daily living conditions for reducing health inequality, which is a major global public health concern. Older public assistance recipients in Japan are socially vulnerable and require healthcare, long-term care, daily living, and social care support. Understanding the diverse daily living needs among public assistance recipient subgroups would prompt the development of novel support measures in the welfare sector. Therefore, this study aimed to understand the daily life needs of older recipient subgroups (segments) created quantitatively in our previous study. We interviewed four caseworkers at municipal welfare offices in 2021; the interview data were analyzed using a qualitative descriptive method to describe the daily life needs of the five older recipient segments for each sex. Five themes of daily life needs were demonstrated: *i*) housing, *ii*) financial, *iii*) welfare service, *iv*) healthcare, and *v*) no daily life needs. Consequently, we identified the daily life needs of some older recipient segments, indicating the necessity for support interventions. Future research would help interview other professionals from various backgrounds to further understand the daily life needs of older recipient segments.

***Keywords*:** public assistance recipients, older people, segmentation, daily life needs, qualitative study

Introduction

Transition from individual-level treatments focusing on modifying people's behaviors to social-level interventions that improve their daily living conditions should be made to reduce health inequality, which is a major global public health concern (*1*). A public assistance program in Japan (*seikatsu-hogo*) is a government-provided social assistance program aimed at ensuring a minimum standard of living for individuals below the poverty line. Qualified households can receive monthly financial assistance alongside complete exemptions from medical and long-term care expenditures. Approximately 1.6% of the population is currently enrolled in this program (*2*). Although public assistance recipients receive equal financial assistance, recent studies have demonstrated health inequalities owing to their individual social backgrounds (*3,4*), thereby indicating that recipients could benefit from additional non-financial support tailored to their needs, including support for daily life.

Older public assistance recipients are more likely to require healthcare, long-term care, daily living, and social care support than younger recipients (*5*). The proportion of households with people aged 65 years or older receiving public assistance is 55.5% in 2023 (*2*). Therefore, older recipients should be the primary target age group for supportive intervention. Since 2021, a healthcare support program has been implemented to provide health and social care to individuals of all ages receiving public assistance in welfare offices. A major challenge in implementing this program is identifying the appropriate targets for intervention and care planning (*6*). Thus, we focused on theories and practices in business and social marketing to provide tailored support interventions. Segmentation involves dividing an entire target group into subgroups (segments) based on their characteristics (*7*). Each segment comprises individuals with similar characteristics and needs. Understanding the diverse daily living needs of older recipients using the segmentation method would provide new support measures in the welfare field.

In this study, we aimed to understand the daily life

needs of older recipient segments, which were created quantitatively by applying the segmentation approach in our previous study (*8*), to offer tailored medical and social support interventions for these segments.

Study design and data collection

Setting and participants

We interviewed caseworkers at municipal welfare offices in Japan from September to October 2021. The caseworkers were local government officials in welfare offices responsible for administrative activities related to processing paperwork for protection applications and conducting interpersonal support through routine home visits. Purposive sampling was used to recruit caseworkers working in two municipal welfare offices (A and B), which had provided data for quantitative analysis in our previous study (*8*). In 2021, Municipality A had a population of 98.927, with 26.2% aged ≥ 65 and 1.8% receiving public assistance. Municipality B had a population of 184,577, with 24.6% aged ≥ 65 and 2.7% receiving public assistance. Participants were recruited from experienced caseworkers with at least 3 years of experience, based on the fact that approximately 60% of caseworkers had less than 3 years of casework experience (*9*). We agreed on data saturation after conducting two joint interviews involving four participants by employing the concept of "information power." The information power is that the number of participants in qualitative interview studies depends on their information, which is relevant to the actual study (*10*).

Data collection

KU (a female physician with 19 years of clinical experience and 4 years of qualitative researcher training) conducted a joint interview with caseworkers *via* video Zoom conference (Zoom Video Communications Inc., U.S.A.). A joint interview is a format between individual interviews and focus groups where interviewees who have a relationship with each other can express their opinions (*11*). We obtained written consent from all interviewees to participate in this study.

We used an interview guide during the interviews (Supplemental File 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=84*). Participants were asked whether they could recall older recipients with similar characteristics from the segments obtained in our previous study (*8*). Subsequently, we asked them to describe the daily life needs of the recipient segment. Participants were asked these two questions about each segment of male older recipients (Supplemental Figure S1a, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=84*) and that of female older recipients (Supplemental Figure S1b, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=84*). The daily life needs of older recipient segments were normative needs defined by caseworkers in relation to norms or desirable standards (*12*). Interviews were conducted, audio-recorded, and transcribed in Japanese.

Data analysis

All the interview data were translated from Japanese to English. We analyzed the data using the qualitative descriptive method (*13*). UK and NK conducted data analysis. After reviewing the verbatim transcripts, text segments were divided into codes. All identified codes were evaluated and compared to determine content overlap and similarity. Codes were classified into subthemes based on their similarities and differences. Themes were generated from these subthemes. To ensure credibility and trustworthiness, all authors discussed and reviewed the transcribed data, subthemes, and themes throughout the process. Subsequently, we sent the findings to the interviewees and asked them to check for any differences from the intended content. MAXQDA 2022 (VERBI GmbH, Berlin, Germany) was used for data analysis.

Ethics approval

The study protocol was approved by the Ethics Committee of the Graduate School and the Faculty of Medicine of Kyoto University (approval no.: R3565) in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Daily life needs of older public assistance recipient segments

Four participants who agreed to be interviewed were recruited (Table 1). Joint interviews were held twice with caseworkers working in Municipalities A and B. The duration of the interview was 85 min for Municipality A and 80 min for Municipality B.

The themes, subthemes, and examples of raw data regarding the daily life needs of older recipient segments for each sex are presented in Table 2 a and b. Five themes of daily life needs were demonstrated: *i*) housing (male Segments 1 and 3), *ii*) financial (male Segment 1 and female Segments 2 and 3), *iii*) welfare service (male Segment 3), *iv*) healthcare (female Segment 5), and *v*) no

Table 1. List of participants

ID	Sex	Municipality	Years of casework experience
1	Male	A	7
2	Male	A	9
3	Male	B	3
4	Male	B	3

daily life (female Segment 4) needs. The participants did not identify any daily life needs in male Segment 2 and female Segment 1. No descriptions of daily life needs were provided for male Segments 4 and 5 because none of the participants answered that they could think of older recipients from these segments.

Housing is widely recognized as an essential social determinant of health (*14*). As mentioned in a subtheme of male Segment 2, a relief facility is defined as "a facility that aims to provide livelihood assistance by accepting recipients who have difficulty leading their daily lives due to significant physical or mental disabilities" (*15*). Relief facilities accept people with mental disabilities who are discharged from mental hospitals and older persons with multiple disabilities or intellectual disabilities and thus serve as a last resort for those who have difficulty finding a place to live (*15*). Hence, caseworkers were concerned that if those in male Segment 2 would not be accepted into the relief facility, they would not be able to find a place to live.

Three segments of older recipients had financial needs. Managing finances is essential for maintaining safe and independent living in older people, yet it often becomes impaired with age. A previous study demonstrated that women, particularly those with a history of stroke, reduced cognitive functioning, and difficulty in activities of daily living had significantly greater difficulty in managing their finances (*16*). The financial needs "not reporting working income" in female Segment 2 are explained by the system requiring caseworkers to receive an income declaration form at least once a month or every 3 months from recipients capable of working (*17*). The program for supporting the improvement of household finances for recipients

Table 2. Daily life needs of each segment of male (a) and female (b) older public assistance recipients

(a)

Segment	Quantitative results	Qualitative results		
		Theme	Subtheme	Examples of raw data
1	Workers	Financial needs	Getting charged a co-payment at the time of hospitalization	*These individuals receive a reduced cost of livelihood assistance when they are hospitalized. In contrast, the amount of their own payment to the hospital arises. As the pension is not sufficient to cover their living expenses, they have to pay for it partially. Therefore, when hospitalized, their standard of living decreases.* (ID 2)
			Being unable to manage rent payments	*Because they can earn their own living expenses to some extent, which means that they can earn the housing assistance portion, they cannot set up a payment by proxy.* (ID 3)
2	Facility residents with disablity	Housing needs	Being unable to live in a relief facility	*Relief facilities are for people who have difficulty living in an ordinary home, but there are some people who cannot easily live there; people whose ADLs have declined considerably, people with mental illness, and people who are not certified as having a mental disability but have difficulty living are unable to live in a relief facility.* (ID 1)
		Daily life needs were not identified by participants.	Daily life needs were not identified by participants.	*Caseworkers may not be aware of their life issues because they notice that people in the facility receive support from other agencies.* (ID 3)
3	People with psychiatric disorders living at home	Housing needs	Not being accustomed to living in a rental house	*When they do not fit well in a rental house, they are too young to move to a facility, so we need to consider support that emphasizes living at home for a longer period of time.* (ID 3)
		Welfare service needs	Refusing to use welfare service for persons with disabilities	*Some people refuse welfare services for persons with disabilities. It is difficult to find appropriate services for them.* (ID 2)
4	People living at home with support	All participants stated that they could not think of older recipients from this segment; therefore, no descriptions of daily life needs were provided.		
5	People who have started using public assistance due to life events	All participants stated that they could not think of older recipients from this segment; therefore, no descriptions of daily life needs were provided.		

Note: The quantitative results were adapted from Reference 8. Adapted with permission.

Table 2. Daily life needs of each segment of male (a) and female (b) older public assistance recipients (continued)

(b)

Segment	Quantitative results	Qualitative results		
		Theme	Subtheme	Examples of raw data
1	Facility residents aged over 85 years with disability, psychiatric disorders	Daily life needs were not identified by participants.	Daily life needs were not identified by participants.	*For those who are in a facility, the facility takes care of their lives; therefore, in a sense, I think we do not give them direct support.* (ID 2)
2	Workers	Financial needs	Not reporting working income	*From our point of view, if they have properly reported the income they have earned, there is no problem.* (ID 1)
3	People living in rental house with support needs	Financial needs	Being unable to manage day-to-day finances	*They have dementia and already start having trouble managing their finances.* (ID 3)
4	People with physical diseases living in public house	No daily life needs	Having no daily life needs	*I wonder if there are relatively few people with life issues.* (ID 1) *I honestly cannot think of their life issues.* (ID 4)
5	People who have started using public assistance due to life events	Healthcare needs	Not seeing a doctor regularly	*We provide assistance for their routine medical visits, but I think it is not so demanding.* (ID 1)

Note: The quantitative results were adapted from Reference 8. Adapted with permission.

has been implemented since 2018 to assist in proposing budget management (*18*). Older recipients are not included in the target population. It is preferable for caseworkers to provide financial management support to them in cooperation with other stakeholders.

In this study, caseworkers did not identify any daily life needs in male Segment 2 and female Segment 1. They stated that older recipients living in the facility received support from care workers and that older recipients on long-term care insurance were supported by care managers (licensed professionals who coordinated the care specified in the care plan and monitored the care process within an individualized budget based on the client's eligibility level). The caseworkers believed that support activities for older recipients were not required when they had already received support from other professionals. When operationalizing the identified segments results, information on whether older recipient segments are provided with support from other professionals will help prioritize the segments that need the most support.

Caseworkers noted that older recipients in female Segment 4 did not have any daily life needs. These recipients appeared to live independently at home. Conversely, some caseworkers may be unable to find the daily life needs of all older recipients due to their enormous workload. The standard allocation for caseworkers in city welfare offices is one per 80 households (*19*). However, in Municipality A, each caseworker was responsible for an average of 96 households; in Municipality B, it was 100. In future research, we can consider interviews with other professionals engaged in support activities for the recipients to verify the segment's daily life needs if caseworkers do not recognize them.

The daily life needs of older recipients were not described by caseworkers in male Segment 4 and 5. Although the finding that none of the caseworkers could recall older recipients from these two segments demonstrated the advantages of machine learning techniques in discovering results that would otherwise be difficult to obtain (*20*), it was not possible to assess the daily life needs of these segments. This issue needs to be addressed in future studies.

To our knowledge, this is the first study to examine the daily life needs of older assistance recipients by segment. Segmentation is often described as "population or patient segmentation" in the medical field and is widely used in different clinical contexts (*21*). However, no previous studies have utilized segmentation in the welfare field. Our approach makes valuable contributions by offering new support measures for welfare care. However, this study has several limitations. First, we collected data only from caseworkers but not from other professionals. Although the participants were experienced caseworkers and were from welfare offices that provided data for creating the segments, it would be better to examine the daily needs of recipients from the other professional's perspective. Second, the transferability of our findings may be limited because we used the segments created from the data of the recipients in two municipalities and interviewed caseworkers working in these two municipalities.

In conclusion, we identified a wide variety of daily

life needs of older recipient segments. Contrarily, the findings revealed that caseworkers did not identify any daily life needs in some segments. Future research would help interview other professionals from various backgrounds further to understand the daily life needs of older recipient segments.

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Travel-associated sexually transmitted infections in Japan: An observational study using imported infectious disease registry data

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Abstract: International travel is a risk factor for acquiring sexually transmitted infections (STIs) owing to factors such as increased sexual opportunities, a sense of freedom, and the allure of the sex industry. We investigated the incidence of travel-associated STIs in Japan using data from the Japan Registry for Infectious Diseases from Abroad (J-RIDA) reported by 17 participating medical institutions between October 2017 and December 2022. Data were collected on the patients' age, sex, nationality, chief complaint, whether they had visited a travel clinic before travel, travel history, and final diagnosis. Of 4545 cases of travel-associated illness reported, 52 (1.1%) were STIs. Most patients with STIs were male (81%) with a median age of 31 years. HIV (17%), genital herpes (13%), syphilis (13%), and gonorrhea (12%) were the most frequently reported STIs. Only one patient had visited a travel clinic before travel. Promoting awareness and vaccination is crucial for preventing travel-associated STIs.

***Keywords*:** sexually transmitted infections, Travel medicine, HIV

Introduction

Sexually transmitted infections (STIs) are a pervasive global public health concern. International travel is associated with an increased risk of acquiring STIs due to the freedom, exoticism, absence of regular partners, and allure of the sex industry, which facilitates new sexual encounters (*1*). Previous studies have reported travel-associated STI incidence rates of 0.9–5.7% (*2*) in patients attending international travel clinics. However, establishing a direct causal link between travel and infection is challenging because STIs have variable incubation periods and are often asymptomatic.

Despite numerous reports on the incidence of travel-associated STIs, limited data are available on the incidence of travel-associated STIs in Japan. According to a previous single-center study by our team, 2.0% of symptomatic patients presenting with travel-associated illnesses were diagnosed with an STI (*3*). Notably, no patients presented with symptoms of urethritis, a recognized common precursor of travel-associated STIs, suggesting that patients with urethritis symptoms sought medical attention elsewhere such as at sexually transmitted disease clinics or urology departments. Thus, collaborative investigations involving multiple healthcare facilities are necessary to obtain precise data on the incidence of travel-associated infections. To address this need, the Japan Registry for Infectious Diseases from Abroad (J-RIDA) was established, with the primary goal of documenting the profile of imported infectious diseases in Japan (*4*). In this study, we reviewed cases of travel-associated STIs registered in J-RIDA to assess the scope of travel-associated STIs.

Study design and data collection

J-RIDA was established as a repository for imported infectious diseases. The study cohort comprised patients with suspected infections acquired overseas, and there were no specific constraints on travel duration. Japanese residents traveling abroad and foreign visitors arriving in Japan were eligible for inclusion in this study. Patients registered in J-RIDA who were diagnosed with travel-associated STIs were included in this study. We used

REDCap, an electronic data collection system, for case registration. This system facilitated the systematic compilation of data from a diverse array of sources.

Case registration commenced in October 2017, with 17 Japanese medical institutions contributing to the database. Information collected during enrollment included patient demographics (age, sex, and nationality), chief complaint, travel history, date of visit, date of onset, whether the patient had visited a travel clinic before traveling, final diagnosis, and patient outcomes. Thirteen diseases were classified as STIs: syphilis, HIV infection, genital *Chlamydia* infection, gonorrhea, genital herpes virus infection, condyloma acuminatum, trichomoniasis, genital candidiasis, hepatitis B, urethritis not otherwise specified, genital ulcer, acute pelvic inflammatory disease, and pubic lice. Other clinician-judged STIs were also included. Acquired immunodeficiency syndrome, herpes simplex infection, chronic pelvic inflammatory disease, and genital warts were excluded due to the extended interval between infection and diagnosis. Hepatitis A, amoebic dysentery, and giardiasis, which can be transmitted both sexually and orally, were also excluded. For HIV, syphilis, and hepatitis B, clinical judgment determined their association with travel.

The study was approved by the National Center for Global Health and Medicine ethics committee (NCGM-G-002328-08) and the ethics committees of each participating institution before case registration started. The study was conducted in compliance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because the study was a retrospective analysis of registry data.

The J-RIDA database is not publicly available, but participating research centers can use the data if the research group agrees. For this study, we obtained authorization from the J-RIDA steering committee to use the data for the purpose of analyzing travel-associated STIs in Japan.

Table 1. Characteristics of patients diagnosed with travel-associated STIs and other travel-associated conditions

Characteristics	Travel-associated STIs (n = 52)	Other travel-associated conditions (n = 4,493)
Age (years), median (range)	31 (26–39)	33 (24–46)
Male	42 (81%)	2,629 (59%)
Nationality (area)		
Japan	21 (40%)	3,256 (72%)
Europe	9 (17%)	217 (5%)
Southeast Asia	8 (15%)	231 (5%)
North America	7 (13%)	125 (3%)
East Asia	5 (10%)	348 (8%)
Africa	2 (4%)	92 (2%)
Other	0	224 (5%)
Country (area) of residence		
Japan	39 (75%)	3,591 (80%)
North America	5 (10%)	109 (2%)
Europe	3 (6%)	162 (4%)
East Asia	3 (6%)	210 (5%)
Southeast Asia	2 (4%)	203 (5%)
Other	0	218 (5%)
Area of visit		
Southeast Asia	29 (45%)	2,165 (37%)
Europe	14 (22%)	532 (9%)
East Asia	9 (14%)	891 (15%)
North America	8 (12%)	260 (4%)
South Asia	3 (5%)	515 (9%)
Africa	1 (2%)	806 (14%)
Other	1 (2%)	625 (14%)
Purpose of visit		
Tourist from abroad	18 (35%)	599 (13%)
Personal travel	12 (23%)	1,283 (28%)
Business	10 (19%)	1,161 (26%)
Immigration	7 (13%)	165 (4%)
Visiting friends and relatives	3 (6%)	314 (7%)
Other	2 (4%)	1,018 (23%)

Epidemiology of travel-associated STI in Japan

During the enrollment period, 4545 patients were enrolled, of whom 52 (1.1%) were diagnosed with an STI and 4,493 were diagnosed with other conditions. Table 1 summarizes the characteristics of the cases. Of the 52 patients diagnosed with an STI, 42 (81%) were male, with a median age of 31 years. The most frequent reasons for travel were tourist from abroad (35%), personal travel (23%), and business (19%). In the patient cohort, 21 patients (40%) were Japanese, and the remaining patients were from various regions: 9 (17%) from Europe, 8 (15%) from Southeast Asia, 7 (13%) from North America, 5 (10%) from East Asia, and 2 (4%) from Africa. Furthermore, 42 patients had travelled to 65 countries, distributed as follows: 45% in Southeast Asia, 14% in East Asia, 5% in South Asia, 22% in Europe, 12% in North America, and 2% in Africa. Among patients diagnosed with non-STIs, 72% were foreign nationals. Compared with patients diagnosed with non-STIs, patients diagnosed with STIs were more likely to be foreign nationals (31/52, 60% *vs.* 1237/4493, 28%). Among the 25 patients with STIs, excluding tourists from abroad, immigrants, and those visiting friends and relatives, only one patient (4%) had visited a travel clinic prior to their departure.

The distribution of STIs is detailed in Table 2. The most frequently diagnosed STIs were to HIV infection (9 cases, 17%), genital herpes (7 cases, 13%), syphilis (7 cases, 13%), and gonorrhea (6 cases, 12%). In addition, 2 cases (4%) of Mpox, an STI that has recently attracted worldwide attention, were reported. Among the 9 patients with HIV infection identified in our study, 4 were foreign nationals and 6 had traveled to other Asian countries. Seven patients had systemic symptoms suggestive of acute HIV infection, including fever and night sweats.

This study reviewed the records of patients diagnosed with travel-associated STIs at 17 medical institutions over a 5-year period. To our knowledge, this is the first multicenter study of travel-associated STIs in Japan. We

Table 2. Distribution of travel-associated sexually transmitted infections reported to the Japan Registry for Infectious Diseases from Abroad (J-RIDA) between October 2017 and December 2022

Infections	Travel-associated STIs (*n* = 52) *n* (%)
HIV Infection	9 (17%)
Genital herpes	7 (13%)
Syphilis	7 (13%)
Gonorrhea	6 (12%)
Acute pelvic inflammatory disease	5 (10%)
Urethritis not otherwise specified	5 (10%)
Hepatitis B	3 (6%)
Genital *Chlamydia* infection	3 (6%)
Mpox	2 (4%)
Condyloma acuminatum	2 (4%)
Genital candidiasis	1 (2%)
Epididymitis	1 (2%)
Bacterial vaginosis	1 (2%)

conducted a comprehensive literature search for other multicenter studies on travel-associated STIs in Japan using PubMed and Ichushi-Web (a Japanese medical literature database). The search strategy for PubMed included combinations of MeSH terms and keywords related to STIs, travel, Japan, and multicenter studies. For Ichushi-Web, we used a similar search strategy with relevant Japanese keywords. Neither the PubMed search nor the Ichushi-Web search yielded any articles that met our criteria for a multicenter study on travel-associated STIs in Japan. These findings support our claim that this study is the first multicenter study to assess the profile of travel-associated STIs in Japan.

Data on the incidence of travel-associated STIs in Japan are inadequate. However, Kuroda *et al.* (*5*) reported that 2% of cases of male urethritis attributed to contact with commercial sex workers (CSWs) were linked to overseas travel. The GeoSentinel Surveillance and Research Network found that urinary tract infections, STIs, and gynecological diseases combined, accounted for 2.9% of health problems among travelers returning from abroad between 2007 and 2011 (*6*). This study found that 1.1% of patients with suspected infection acquired during travel to other countries were diagnosed with STIs, which is consistent with the proportion reported in studies from other countries.

Only one patient had visited a travel clinic before travel. Thus most travelers missed the opportunity for preventive measures such as hepatitis B vaccination, which is recommended for people traveling to high-prevalence regions for an extended period. Travel clinics can also provide education on STI prevention during pre-travel visits.

One characteristic of this study is that patients diagnosed with travel-associated STIs were more likely to be foreigners (31/52, 60%) than those diagnosed with other travel-associated conditions (1,237/4,493, 28%). Many STIs were diagnosed among travelers to Japan or immigrants seeking medical care. A previous investigation revealed that foreign nationals constituted 23.6% of the imported infectious disease cases recorded in J-RIDA-registered institutions. The elevated proportion of foreign patients in our study may stem from the limited availability of clinics that cater to foreign patients with suspected STIs. As the number of foreign nationals visiting Japan is likely to continue to increase, addressing the scarcity of clinics accessible to foreign visitors and enhancing education regarding appropriate STI management at clinics providing services for international visitors are pressing concerns.

Despite the availability of effective antiretroviral therapy, HIV infection remains an important STI concern. Developing countries, particularly those in Sub-Saharan Africa and Southeast Asia, face high rates of HIV infection compared with developed countries, including Japan. In developing countries HIV transmission is predominantly through heterosexual intercourse, whereas in the United States and Europe, it is primarily associated with homosexual contact and injection drug use. Consequently, both male and female travelers engaging in sexual activities while abroad should be made aware of the risk of HIV infection. In Southeast Asia, including Thailand and in African countries, HIV prevalence among CSWs is high. HIV incidence rates among CSWs in Southeast Asia range from 0.23 to 27.8 per 100 person-years (*7*). The prevalence of HIV infection among international travelers with STIs ranges from 2.2% to 27.4% (*8,9*). In Japan, 82.8% of the new HIV infections reported in 2019 were sexually transmitted, with 17.1% of Japanese men and 23% of Japanese women infected through heterosexual sex while traveling abroad (*10*). In this study, HIV was the most frequently diagnosed travel-associated STI, highlighting the importance of HIV testing in individuals who engage in high-risk sex during foreign travel. However, tests were not conducted to ascertain whether the cases of HIV identified were of recent onset, and we cannot rule out the possibility of domestic exposure.

In our study, two patients were diagnosed with Mpox, an STI that has attracted global attention recently. Mpox is caused disease by the monkeypox virus, which belongs to the genus *Orthopoxvirus*. It was first identified in humans in 1970 in the Democratic Republic of Congo. Since May 2022, cases of Mpox, which is endemic to central and West Africa, have been reported worldwide (*11*). Most cases are in men, with particularly men who have sex with men. During 2023, the number of reported Mpox cases continued to rise, raising concerns about potential future increases. Although the vaccines are effective in preventing Mpox, it is essential to provide individuals at risk of Mpox infection with information on measures, such as adherence to hand hygiene and condom use.

This study has several limitations. First, we did not investigate whether patients with travel-associated

STIs engaged in sexual activity during travel and did not collect information on sexual behavior, condom use, or sexual partners. This information is crucial for establishing a link between STIs and travel. Second, as data are derived solely from J-RIDA cases, there are no denominator data for all travelers. Consequently, calculating STI incidence rates among travelers or providing risk estimates for specific destinations is not possible. The study passively enrolled travelers seeking care for symptomatic infections and cannot quantify the incidence of travel-associated STIs, as affected travelers may be unaware of infections or perceive them as minor, forgoing medical treatment. This phenomenon particularly applies to infections that are typically asymptomatic, such as *Chlamydia*. Third, participating medical institutions were predominantly university and large urban hospitals focused on acute care. Patients with mild symptoms, such as urethritis, may visit STI clinics or urology and gynecology departments. Fourth, the lack of consistent diagnostic algorithms or standardized procedures for diagnosing STIs is another limitation. The J-RIDA system relies on experienced clinicians making diagnoses and defining diseases as associated with travel, but they do not have standardized diagnostic algorithms. Consequently, the observed high incidence of HIV infection among unwell travelers should be interpreted with caution. Finally, our definition of STIs included conditions such as hepatitis B and syphilis, for which establishing a link to travel can be difficult. These limitations may have led to an overestimation of the overall incidence of STIs among travelers.

In conclusion, the incidence of travel-associated STIs in Japan is comparable to that reported in other countries, highlighting the global nature of this issue and the need for a consistent management approach. When treating patients with travel-associated illness, healthcare providers should be vigilant for the presence of STIs and adopt a discreet and considerate approach when inquiring about sexual behavior. Early detection, appropriate treatment, and prevention of further transmission are crucial. Collaborative studies involving diverse institutions are necessary to obtain precise data on the incidence of travel-associated STIs. Additionally, establishing a system that increases awareness and educates travelers about STI prevention and appropriate vaccination prior to travel is essential.

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A retrospective single institutional analysis of outpatient chemotherapy in patients with cancer during the COVID-19 pandemic

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Abstract: Providing treatment to patients with cancer, even during the coronavirus disease (COVID-19) pandemic, is essential. In collaboration with infectious disease specialists, we established guidelines for the management of patients with cancer receiving ambulatory treatment during the pandemic on April 8, 2020. This study examined the practice and management of ambulatory chemotherapy under emergency conditions. Following the guidelines, our Breast and Medical oncology department developed a chemotherapy strategy for the phases. Additionally, to distinguish fever during chemotherapy, we developed a flow chart for fever. As part of a fact-finding survey, the status of outpatient chemotherapy was investigated: (1) whether there was any change in the number of chemotherapies before and after the declaration of a state of emergency by the Tokyo Metropolitan Government and (2) the frequency and severity of febrile neutropenia (FN) cases. Compared to before the first declaration of the state of emergency, the number of chemotherapies decreased except after the declaration, but no decrease was observed during the rest of the period; no difference was observed in the frequency or severity of FN outbreaks or in the use of pegfilgrastim for primary prevention before and after the epidemic. With appropriate treatment guidelines, routine chemotherapy can be performed in an outpatient setting during an outbreak.

***Keywords*:** COVID-19, coronavirus, cancer, chemotherapy, breast cancer, outpatient

Introduction

It is important to provide medical care without stopping cancer screening and treatment during an unknown infectious disease pandemic, such as COVID-19. However, there were no treatment guidelines at the beginning of the pandemic, which caused confusion among healthcare providers. Many information and states (*1-3*) from not only Japan but also other countries were submitted. Regardless of the source of information, the basic policy was the same: patients who should avoid treatment interruptions should continue chemotherapy during the COVID-19 pandemic, while patients with stable disease who could continue treatment without face-to-face consultations to reduce the frequency of visits to the hospital.

We established guidelines for the management of patients with cancer receiving ambulatory treatment during the pandemic in April 2020. This study examined the practice and management of ambulatory chemotherapy under emergency conditions.

Activities in our department since the COVID-19 pandemic

Development of treatment guidelines

At the beginning of the COVID-19 pandemic, our outpatient treatment center was divided into three phases according to the number of patients requiring oxygen administration and the number of patients on ventilators. Treatment strategies were established for each phase (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=88*). In Phase 1, the usual medical care was continued; in Phase 2, the usual medical care was reduced to 60%–80%; in Phase 3, the usual medical care was discontinued, and the Ambulatory Treatment Center (ATC) was closed. In addition, the department established guidelines for chemotherapy (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=88*) according to these phases. During preoperative and postoperative

chemotherapy, patients with metastatic breast cancer continued to receive treatment according to the schedule. In contrast, patients with relatively stable diseases visited the hospital less frequently to prevent infection.

Creation of a flow chart for responding to febrile illness

Depending on the causative microorganism, FN is a highly lethal adverse event in cancer chemotherapy (*4*). Therefore, identifying fever during treatment is important. Our department prepared a "Fever Handling Flow" (Figure 1) for outpatient chemotherapy classified according to the FN risk of the regimen. Patients receiving high-risk FN regimens (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=88*) were prescribed an antibiotic (LVFX: levofloxacin) at initial administration to manage their FN at home.

Creation of COVID-19 vaccination procedures in patients with cancer

Patients with cancer are at a high risk of severe disease when they contract COVID-19 (*5*), and patients with cancer under treatment were identified as priority candidates for COVID-19 vaccination (*6*). Various guidelines (*2,7-9*) reported that COVID-19 vaccination should be considered prospectively, so to differentiate between vaccine- and treatment-induced fever, our department developed a procedure for COVID-19 vaccination in patients with cancer (Supplemental Table S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=88*).

Research on outpatient chemotherapy during the COVID-19 pandemic

Evaluation of outpatient chemotherapy performance

We evaluated the number of chemotherapies administered at the ATC of the Department of Breast and Medical Oncology at the National Center for Global Health and Medicine, Tokyo, Japan. We evaluated for 30 days before and after the first (April 7, 2020), second (January 8, 2021), third (April 25, 2021), and fourth (July 12, 2021) declarations of emergency in Tokyo. The first period (Period 1; P1) is from March 8, 2020, to May 6, 2020. The second period (Period 2; P2) is from December 9, 2020, to February 6, 2021. The third period (Period 3; P3) is from March 26, 2021, to May 24, 2021, and the fourth period (Period 4; P4) is from June 12, 2021, to August 10, 2021. We evaluated the type of cancer, stage of disease, number of chemotherapies, regimens, and changes in treatment strategy (changes in regimen and discontinuation) related to the pandemic, presence of fever, and COVID-19. The exclusion criteria were as follows: *i*) patients who did not receive chemotherapy within 60 days before the emergency declaration, *ii*) Patients who participated in a clinical trial. All information was retrieved from electronic medical records.

Research regarding whether the frequency of FN occurrence changed before and after the COVID-19

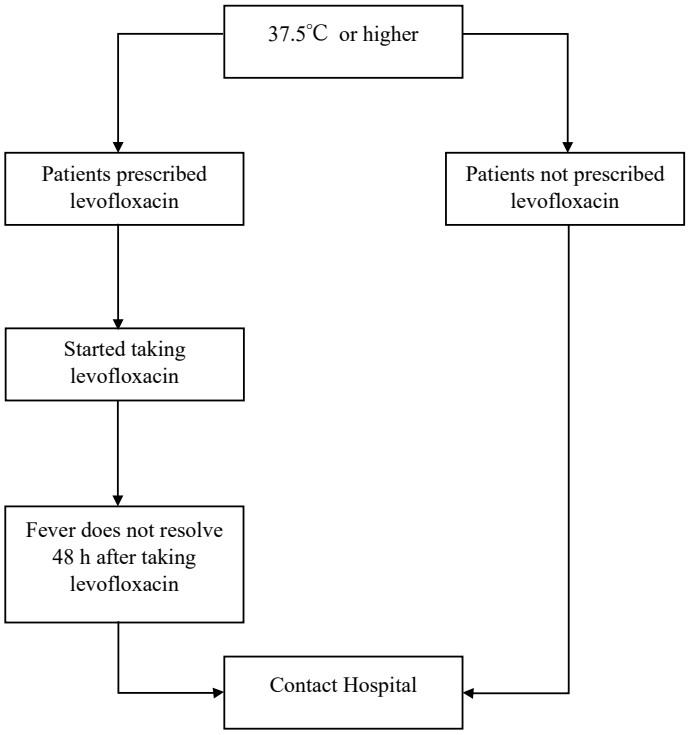

Figure 1. Flow chart for handling fevers established by our department.

pandemic in patients on high-risk FN regimens

The differentiation of fever during treatment is important. The target period was February 1, 2019, to January 31, 2020 (Period 5; P5) before the pandemic and February 1, 2020, to January 31, 2021 (Period 6; P6) after the pandemic. In patients with breast cancer on preoperative and postoperative chemotherapy who received a high-risk FN regimen (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=88*), we retrospectively investigated whether there were changes in the number of FN cases, response to FN (use of prophylactic antimicrobial or pegfilgrastim [Peg-G-CSF] primary prevention for FN), frequency and severity of FN, and number of patients with COVID-19.

These studies were performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the National Center for Global Health and Medicine, Tokyo (Date: March 20, 2020; No. NCGM-G-003481-01).

Evaluation of outpatient chemotherapy performance

The number of eligible patients was 131, 133, 150, and 157 in P1 to P4, respectively (Table 1). The number of chemotherapy sessions was 303, 319, 376, and 409 in P1 to P4, respectively, decreasing after the declaration (112 times) compared with before the declaration of emergency status (191 times) in P1. The number of patients for whom treatment was (or could have been) changed was 27, two, three, and eight in P1 to P4, respectively. Fever was observed in eight, nine, six, and 20 patients (including 10 with adverse reactions to the COVID-19 vaccine) from P1 to P4. None, one, one, and two patients with COVID-19 infection in P1 to P4 and one patient in P3 had moderate or severe COVID-19 symptoms and received hormone therapy.

After the COVID-19 pandemic, the frequency of FN changed in patients on high-risk FN regimens

A total of 93 patients (64 in period 5 and 29 in period 6) were included in the study. The total number of regimens administered was 317 (P5: 226, P6: 91), the number of FN cases (including suspected FN) was 32 (10%, P5: 26 [12%], P6: six [6.6%]), and the number of FN cases requiring hospitalization was four (1.3%, P5: four [1.3%], P6: none [0%]). The number of chemotherapy regimens using Peg-G-CSF for primary prevention was eight (2.5%, P5: eight [2.5%], P6: none [0%]), and there was no significant difference between the periods. The number of FN (or suspected FN) cases was one patient whose regimen was pertuzumab plus trastuzumab plus docetaxel in P5 and one patient who received docetaxel plus cyclophosphamide in P6. All other patients' regimens were doxorubicin plus cyclophosphamide. The number of patients with FN treated with doxorubicin and cyclophosphamide was comparable to that reported in a previous study (9%) (*10*).

Discussion

According to the declarations, the number of chemotherapy sessions was affected in P1 but not in P2 to P4. This is consistent with the results of a previous study (*11*) and may be due to the pandemic, which caused a shortage of personal protective equipment (PPE) which are essential for healthcare providers when administering chemotherapy. In P2, with the first reason for this being P1, the number may have decreased owing to the lack of treatment guidelines, both institutional and professional. The fact that the number of chemotherapy treatments recovered after the treatment guidelines were established suggests that familiarity with the basic policy and the establishment of treatment guidelines at individual facilities may help healthcare providers provide medical care to patients without confusion during a pandemic. Second, PPE, such as masks and gowns, were in short supply, and the environment for medical care needed to be more conducive in P1. Third, after the first declaration, people were more cautious about the unknown virus, and patients might have restricted themselves from going out for hospital visits.

Of the patients who had COVID-19 during the study, only one had moderate or severe symptoms and was undergoing hormonal therapy for breast cancer. This patient did not meet any of these criteria that is reported in previous studies (*12*). It is also important to proceed with cancer treatment without unnecessary fear because COVID-19 does not necessarily cause severe disease even if the patient is immunosuppressed while receiving cytotoxic anticancer drugs.

This study found no differences in the frequency or severity of FN occurrence, preventive use of antimicrobials, or Peg-G-CSF in high-risk FN regimens by period. The frequency of FN with doxorubicin plus cyclophosphamide was similar to that reported previously. This suggests that FN treatment can be continued during the COVID-19 pandemic without special measures. Peg-G-CSF acts on neutrophil progenitor cells to promote neutrophil differentiation. Because lymphocyte counts have been reported to decrease during COVID-19 infection (*13*), Peg-G-CSF is unlikely to be useful for active use other than in identifying fever, even in light of its mechanism of action.

Our study had two limitations. First, because it was conducted at a single institution or department, it was limited to the target population and needed more generality. Second, the proportion of patients with COVID-19 among eligible patients during the study period was small. The number of positive COVID-19 cases in the country increased after the sixth wave (January 1, 2022). However, this period was outside the

Table 1. Chemotherapy-related outpatient treatment implementation status

(A)

Characteristics	P1 (*n* = 131)	P2 (*n* = 133)	P3 (*n* = 150)	P4 (*n* = 157)
Age, median [interquartile range], years	58 [28–88]	57 [29–89]	55 [29–89]	56 [29–89]
Type of Cancer				
Breast cancer	122 (93%)	129 (97%)	145 (97%)	152 (97%)
Gynecologic cancer	7 (5.3%)	4 (3.0%)	5 (3.0%)	5 (3.0%)
Others	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Stages of disease				
NAC or adjuvant	43 (33%)	35 (26%)	48 (32%)	56 (36%)
Palliative	88 (67%)	98 (74%)	102 (68%)	101 (64%)
Number of chemotherapeutic regimens	137	140	164	167
NAC or Adjuvant	48 (35%)	39 (28%)	57 (35%)	59 (35%)
Palliative	89 (65%)	101 (72%)	107 (65%)	108 (65%)
Number of chemotherapeutic times	303	319	376	409
Percentage of chemotherapeutic times※	62%	58%	61%	61%
Before the declaration	191 times (39%)	157 times (28%)	194 times (32%)	192 times (28%)
NAC or Adjuvant	72 (15%)	49 (9%)	69 (11%)	83 (12%)
Palliative	119 (24%)	108 (20%)	125 (20%)	109 (16%)
After the declaration	112 times (23%)	162 times (29%)	182 times (30%)	217 times (32%)
NAC or Adjuvant	50 (10%)	60 (11%)	64 (10%)	94 (14%)
Palliative	62 (13%)	102 (18%)	118 (19%)	123 (18%)

(B)

Characteristics	P1 (*n* = 131)		P2 (*n* = 133)	
Number of patients who changed (or may have changed) treatment※	27 (21%)		2 (1.5%)	
	NAC or Adjuvant	Palliative	NAC or Adjuvant	Palliative
	9 (6.9%)	18 (14%)	0 (0%)	2 (1.5%)
Change of regimens	0 (0%)	3 (2.3%)	0 (0%)	0 (0%)
Extention of interval	2 (1.5%)	4 (3.1%)	0 (0%)	2 (1.5%)
Skip of therapy	1 (0.76%)	4 (3.1%)	0 (0%)	0 (0%)
Postponement of treatment initiation	3 (2.3%)	6 (4.6%)	0 (0%)	0 (0%)
Prescription by telephone	3 (2.3%)	2 (1.5%)	0 (0%)	0 (0%)
Others	3 (2.3%)	1 (0.76%)	0 (0%)	0 (0%)
Number of patients with fever	8 (6.1%)		9 (6.8%)	
Number of patients with COVID-19	0 (0%)		1 (0.75%)	

(C)

Characteristics	P3 (*n* = 150)		P4 (*n* = 157)	
Number of patients who changed (or may have changed) treatment※	3 (2.0%)		8 (5.1%)	
	NAC or Adjuvant	Palliative	NAC or Adjuvant	Palliative
	0 (0%)	3 (2.0%)	1 (0.64%)	7 (4.5%)
Change of regimens	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Extension of interval	0 (0%)	2 (1.3%)	0 (0%)	1 (0.64%)
Skip of therapy	0 (0%)	1 (0.67%)	0 (0%)	6 (3.8%)
Postponement of treatment initiation	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prescription by telephone	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Others	0 (0%)	0 (0%)	1 (0.64%)	0 (0%)
Number of patients with fever	6 (4.0%)		20 (13%)	
Number of patients with COVID-19	1 (0.67%)		1 (1.3%)	

In the case of oral medications, we counted the number of prescriptions as the number of chemotherapies. The percentage of chemotherapeutic times was calculated based on the total number of patients and the number of chemotherapeutic times. ※The total does not add up because of overlapping element. Abbreviation: NAC, Neoadjuvant chemotherapy. COVID-19, Coronavirus disease 2019.

study's coverage period.

The COVID-19 pandemic has allowed healthcare providers to consider the actions that should be taken in the event of a pandemic. With limited information available, hospital guidelines were developed, and their implementation did not result in any serious problems. When a similar situation arises in the future, developing guidelines and triages within the information available at the time can help healthcare providers and patients make appropriate decisions. As the pandemic progresses, it is important to continue providing cancer treatment while considering the risks and benefits for individual patients.

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Association between the paracaval branches of the caudate lobe and the three major hepatic veins in liver casts: Locating the cranial boundary of the caudate lobe

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Abstract: According to Couinaud's definition, the cranial boundary of the caudate lobe is delineated by the three major hepatic veins. However, many branches of the caudate lobe go through the ceiling that is composed of these hepatic veins. The cranial boundary of the caudate lobe should be determined by employing the portal segmentation. We conducted a study based on the dissection of 37 colored resin liver casts to reveal the caudate branches of the liver. The paracaval portal vein branches (PCPvs) were defined as cranial portal branches from the main trunk or first-order branch of the portal vein distributed in front of the inferior vena cava, according to Kumon's classification. The PCVs were traced to reveal the cranial boundary of the caudate lobe. Results showed that in 18 cases (49%), the PCPvs reached the liver surface through the gap between the right and middle hepatic veins (type RM, n = 11), between the tiny branches of the middle hepatic vein (type M, n = 4), and between the middle and left hepatic veins (type ML, n = 3). The PCPvs did not reach the liver surface in 19 cases (type 0). No PCPvs reached the hepatic surface behind the right hepatic vein. Half of the PCPvs in the liver reached the hepatic surface beyond the boundary composed of the three major hepatic veins. Recognition of the PCPvs in the liver is indispensable to perform anatomically precise liver resections involving the major hepatic veins.

Keywords: caudate lobe, major hepatic vein, portal vein, cranial boundary, paracaval portal vein branches

Introduction

According to Couinaud's classification, the caudate lobe is located deep within the liver in front of the inferior vena cava (IVC), cranial to the hilar plate, and beneath the major hepatic veins (*1*). Therefore, a surgical resection of the caudate lobe for hepatic tumors is technically demanding and an anatomically accurate knowledge of the caudate lobe boundary is indispensable (*2,3*). A combined resection of the caudate lobe and other hepatic segments has become a standard step in the treatment of hilar cholangiocarcinoma to eradicate cancer lesions and improve patient survival (*4,5*). Recent advances in minimally invasive hepatectomy have made it possible to resect tumors in the caudate lobe using a laparoscopic or robotic approach (*6*). However, the definition of total caudate lobectomy is ambiguous, and the technical difficulty of a caudate resection varies according to the location of the tumor.

Couinaud defined the caudate lobe of the liver as one of eight segments and further categorized it into two parts, namely segment I and IX or segments IL and IR, based on the spatial position of the lobe behind the major hepatic veins (*7*). However, he abandoned his classification owing to the complexity of crossing glissonean branches in these segments (*8*). Conversely, in this study, we have defined the caudate lobe based on hepatic portal vein segmentation, i.e., the caudate portal venous branches are dorsal branches from the main trunk or from the first-order branches of the portal vein covering the hepatic region in front of the IVC (*9-11*), classifying it into three parts: the Spiegel lobe, the paracaval portion (PC) and the caudate process.

There is no consensus on the boundary of the caudate lobe, especially in relationship to the major hepatic veins. We dissected 37 colored resin hepatic casts to determine the relationship between the caudate lobe branches and the major hepatic veins.

Research design and sample size

The samples included in this study comprised 75 liver

casts prepared between July 1, 1981 and October 2, 1990 (*8-10*). The methods used to prepare the casts have been described previously (*10,11*). Casts weighing ≤ 400 g, with incomplete peripheral branches, damaged IVC or hepatic veins, or incomplete injection of resin were excluded; finally, 37 casts were included in this study.

The dissection of the peripheral branches was performed as described previously (*10,11*). We used forceps with fine tips and gently extracted the small Glissonean and venous branches, piece by piece. High-pressure water was sometimes used to clean up small branches, but was not suitable for revealing small peripheral branches. In some liver casts, the middle hepatic vein or right portal vein were divided to reveal the paracaval portal vein branches (PCPvs) and short hepatic veins. The final lateral view of the liver depicts the remnant left liver after right hemihepatectomy.

We used two cameras to capture stereoscopic photographs of the hepatic branches so that the readers could observe the liver casts three-dimensionally. The distance between the two cameras was 6.5 cm.

This study was approved by the National Center for Global Health and Medicine Research Ethics Committee/Institutional Review Board (approval number: NCGM-S-004739-00).

Relationship between PCPvs and the three major hepatic veins

The number of PCPvs was one in 34 cases and two in three cases. The PCPvs reached the hepatic surface through the ceiling that was composed of the major hepatic veins in 18 of 37 cases (48.6%). The relationship between PCPvs and the three major hepatic veins could be classified into four types.

i) Type RM: PCPvs reached the hepatic surface through the gap between the right and middle hepatic veins (n = 11) (Figure 1A and Figure 2A).

ii) Type M: PCPvs reached the hepatic surface through the branches of the middle hepatic vein (n = 4) (Figure 1B and Figure 2B).

iii) Type ML: PCPvs reached the hepatic surface through the gap between the middle and left hepatic veins (n = 3) (Figure 1C and Figure 2C).

iv) Type 0: The PCPvs did not reach the hepatic surface (n =19) (Figure 1D and Figure 2D).

Among the 15 cases of RM and M types, the root of the PCPvs originated from the right portal vein in six cases, and the left portal vein in nine cases.

No PCPvs reached the hepatic surface behind the right hepatic vein.

Locating the cranial boundary of the caudate lobe

In the present study, we found that PCPvs reached the liver surface in 48.6% of cases through the major hepatic veins. However, no PCPvs reached the liver surface behind the right hepatic vein. This is because we defined the caudate branch as the dorsal branch from the first-order portal vein branches, and did not include branches toward the IVC from the anterior or posterior sections. However, defining PCPvs as branches from the first-order or main branch of the portal vein in the context of portal vein-based liver segmentation is essential for understanding hepatic anatomy (*9-11*). Some PCPvs passed through the gap between the middle and left hepatic veins. Considering the anatomical structures of the PC vein and its branches, liver surgeons should encounter PCPvs behind the middle hepatic vein during conventional hemihepatectomies. Alternatively, systematic segmentectomy of segment 8 should involve resection of the PCPvs when the surfaces of the IVC, middle hepatic vein and right hepatic vein are exposed on the resectional plane. We believe that it is essential for all liver surgeons to determine the distribution of the caudate lobe branches among the major hepatic veins.

It has been reported that part of the liver surface is supplied by the portal vein branches of the caudate lobe. By examining 23 liver casts, we have previously reported that in 50% of cases the PCPvs reached the hepatic surface (*9,10*). Couinaud reported that PCPvs penetrated the plane comprising the major hepatic veins in 40 casts, and that in 18 of these (45%) the PCPvs reached the hepatic surface (*7*). Maki et al. revealed that the caudate lobe can be identified on the liver surface using 3D Vincent analysis of dynamic computed tomography (CT) scan images in 30.2% of cases (*12*). In order to locate the cranial boundary of the caudate lobe, it is essential to define the PCPvs clearly.

In this study, we found that 8% of PCPvs went through the gap between the middle and left hepatic veins and 11% went through the branches of the middle hepatic vein. These branches can be exposed during hepatectomy; however, without knowledge of our current data, surgeons would not be aware that the tiny portal vein branches between the middle and left hepatic vein originated from the PC portion of the liver. These fine portal vein branches cannot always be visualized even on a precise dynamic CT scan.

A partial or total caudate lobectomy is often performed during hemihepatectomy to resect hepatic or biliary malignancies. An anatomically precise definition of the right-sided boundary of the caudate lobe is important in cases of right hemihepatectomy for liver cancer or extended left hemihepatectomy for biliary cancer. It is technically possible to preserve the liver PC portion during right hemihepatectomy (*13*). On the other hand, it is important to remove the PC portion to enhance the curability of perihilar cancer (*4,5*). Liver surgeons must accurately define the right-sided and cranial boundary of the caudate lobe to perform anatomically precise liver resections.

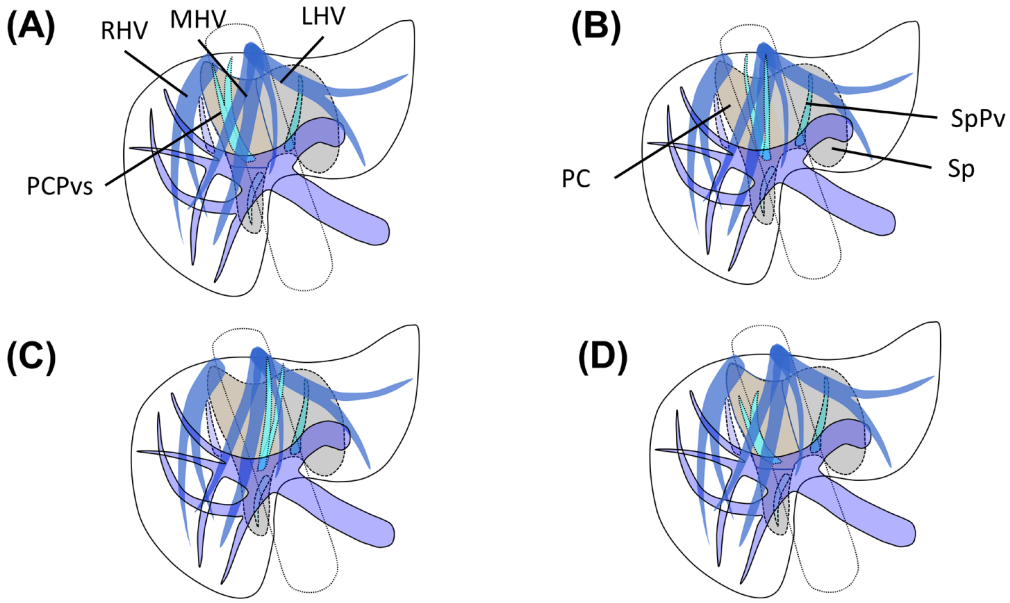

Figure 1. Four types of relationships between the PCPvs and the major hepatic veins. (A) Type RM, PCPvs reach the hepatic surface through the gap between the right and the middle hepatic veins (MHV); **(B)** Type M, PCPvs reached the hepatic surface through the branches of the MHV; **(C)** Type ML, PCPvs reached the hepatic surface through the gap between the MHV and left hepatic vein; **(D)** Type 0, PCPvs did not reach the hepatic surface. PCPvs, paracaval portal veins; RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; PC, paracaval portion; Sp, Spiegel lobe; SpPv, Spiegel portal vein.

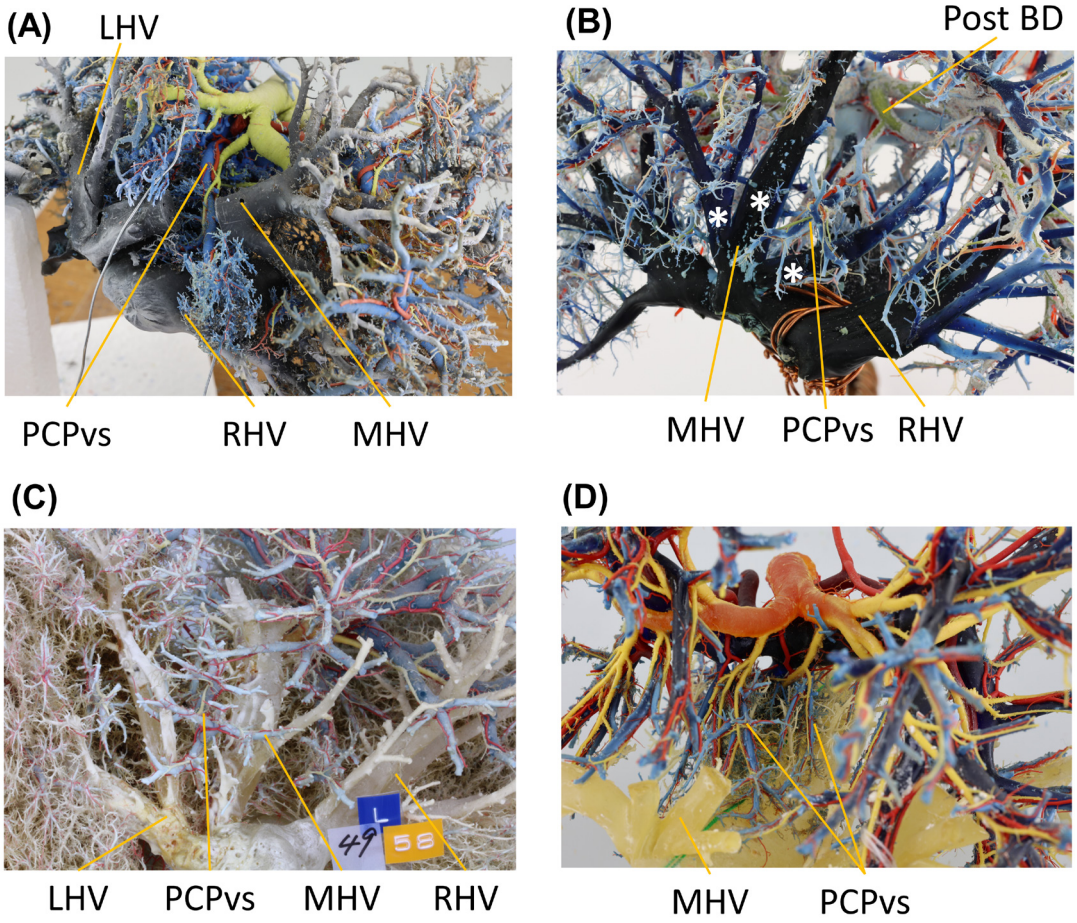

Figure 2. (A) Right-cranial view of a whole liver cast of type RM. The PCPvs extends from the left portal vein toward the liver surface behind the gap between the MHV and RHV. The MHV was divided to reveal the PCPvs clearly. **(B)** Right-cranial view of a whole liver cast of type M. The PCPvs originating from the left portal vein penetrated the plane of the MHVs and reaches the liver surface. **(C)** Right-cranial view of a whole liver cast of type ML. The penetrating PCPvs passed through the gap between the MHVs and the LHVs toward the liver surface. **(D)** Cranial view of a whole cast of Type 0. The caudate lobe was small and the PCPvs did not reach the liver surface. PCPvs, paracaval portal veins; RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; PCB, paracaval bile duct; RHD, right hepatic duct; Post BD, posterior bile duct.

In conclusion, we dissected 37 liver casts and focused on the relationship between PCPvs and the major hepatic veins. In half of the cases, the PCPvs passed through the gap between the major hepatic veins and reached the hepatic surface; however, there were no branches behind the right hepatic vein. This anatomical knowledge will be indispensable for liver surgeons in the era of minimally invasive hepatectomies.

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Prospective therapeutic studies of disseminated extranodal large B-cell lymphoma including intravascular large B-cell lymphoma

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Abstract: This study aimed to establish a standard treatment for disseminated extranodal large B-cell lymphoma, including intravascular large B-cell lymphoma (DEN-LBCL/IVL), and to validate the clinical diagnostic criteria we proposed. Between 2006 and 2016, 22 patients were enrolled in a clinical trial conducted by the Hokuriku Hematology Oncology Study Group. The first cycle of chemotherapy consisted of dose-reduced cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with delayed administration of rituximab. From the second to the sixth cycle, patients received conventional rituximab and CHOP therapy. The primary endpoint was overall survival (OS), while the secondary endpoints included the complete response (CR) rate and time to treatment failure (TTF). The results showed a CR rate of 73%, a median OS of 65 months, and a median TTF of 45 months. These findings indicate that patients with DEN-LBCL/IVL were effectively treated with our new chemoimmunotherapy regimen. Our clinical diagnostic criteria are useful for identifying patients who require early intervention.

***Keywords*:** intravascular large B-cell lymphoma, random skin biopsy, R-CHOP, clinical diagnostic criteria

Introduction

Intravascular large B-cell lymphoma (IVL) was first documented by Pfleger and Tappeiner in 1959 (*1*). IVL is defined as a subtype of diffuse large B-cell lymphoma (DLBCL) and recognized in the 2017 WHO classification (*2*). An Asian variant characterized by hemophagocytic syndrome was established by Murase *et al.* (*3*). Most IVL studies involve small, retrospective case analyses. A large-scale prospective study is needed to evaluate treatment protocols. IVL diagnosis is limited to cases with confirmed occlusion of vascular lumens by neoplastic B-cells. However, some cases with diffuse large lymphoid cell proliferation in the bone marrow (BM) without clear masses might still originate from IVL. These include primary BM DLBCL or disseminated extranodal DLBCL (DEN-LBCL) without masses. Patients with pathologically confirmed IVL and those with clinically suspected IVL would experience similar rapidly deteriorating clinical courses, which could lead to death. Recently, Suzuki *et al.* (*4*) reported no significant differences in characteristics and prognosis between IVL expressing PD-L1 and extranodal lymphomas. Early clinical diagnostic criteria for DEN-LBCL/IVL have been reported to be useful for diagnosis (*5*), and random skin biopsy (RSB) and BM biopsies are recommended (*6*). Most IVL patients present with multiple organ involvement and are classified as Stage IV according

to the Ann Arbor classification. They also have high-risk scores on the International Prognostic Index (IPI) (*7*). Standard treatment for DLBCL, such as CHOP chemotherapy (*8*), is considered for IVL. Anthracycline-based chemotherapy has shown effectiveness (*9*). Murase *et al.* (*10*) reported that patients treated with non-anthracycline-based chemotherapy had a poor prognosis. Rituximab-containing chemotherapy significantly improved outcomes in Japanese patients (*11*). To reduce the risk of infusion reactions, rituximab should be administered after debulking with CHOP. For patients expected to have severe bone marrow suppression due to BM infiltration, a reduced CHOP dose is recommended initially. We developed a new protocol with reduced-dose CHOP followed by rituximab and evaluated its efficacy. Additionally, we assessed early clinical diagnostic criteria and pathological diagnostic rates, and report these findings.

Study methods and analysis

In this study, patients aged 20 years or older with primary DEN-LBCL/IVL were enrolled, confirmed pathologically or meeting clinical diagnostic criteria (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Rapidly progressive cases began treatment based on clinical diagnosis. Exclusion criteria included suspected connective tissue disease/vasculitis, severe infections, prior chemotherapy, human immunodeficiency virus (HIV), human T-cell leukemia virus type 1 (HTLV-1), and hepatitis B virus (HBV) antigen positivity, among others. Written informed consent was obtained, the trial was approved by institutional review boards, registered in the UMIN Clinical Trials Registry (ID: 000001309), and conducted in accordance with the Declaration of Helsinki.

The first chemotherapy cycle involved two-thirds of the conventional dose of each CHOP drug, except for prednisolone. Rituximab was administered on day 7 if CD20 expression was confirmed. Dosage adjustments were permitted for patients with BM suppression, poor performance status (PS), or advanced age. From the second to sixth cycles, conventional R-CHOP therapy was given. Criteria for continuing to the second cycle included fever reduction, PS improvement, LDH normalization, and neutrophil count recovery. Treatment was discontinued if criteria were not met by day 28. After six R-CHOP cycles, peripheral blood stem cell (PBSC) harvesting was performed for younger patients (< 70 years) or those with improved PS. High-dose chemotherapy with autologous PBSC transplantation (autoPBSCT) followed PBSC harvesting. In older patients (≥ 70 years) or those with poor PS, additional chemotherapy with high-dose methotrexate (MTX) and rituximab was administered to prevent central nervous system (CNS) recurrence and improve prognosis. The protocols for PBSC harvesting and high-dose chemotherapy combined with autoPBSCT were not specified in this study. Preventative measures included sulfamethoxazole/trimethoprim to prevent Pneumocystis infection and additional antifungal agents. Patients positive for hepatitis B core or surface antibodies were monitored monthly for HBV-DNA and treated with antiviral agents if needed.

IVL rarely forms masses, so we created our own response evaluation criteria (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). The primary endpoint was overall survival (OS), with secondary endpoints including complete remission (CR) rate, concordance rate between clinical diagnosis and pathologically confirmed diagnosis in clinically diagnosed patients, diagnostic yields of BM and RSB, and time to treatment failure (TTF). TTF was the interval from enrollment to disease progression or death. OS and TTF were analyzed using the Kaplan-Meier method.

Clinical trial outcomes and diagnostic evaluations

Patient characteristics

A total of 22 patients were recruited from six medical institutions between March 2006 and March 2016. There were 12 men and 10 women, with a median age of 74 years (range 52–89 years) (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). The median follow-up for survivors was 35 months.

Survival and treatment outcomes

Six patients (38%) experienced recurrence, two of whom received salvage treatment and survived (117 and 124 months). Eleven patients died; five died during treatment before CR confirmation. Causes of death included pneumonia (n = 1), sepsis (n = 1), multiple organ failure (n = 2), and disease progression (n = 1). Four died after recurrence, and two in remission from complications. Median OS and TTF were 65 and 46 months, respectively (Figure 1A.1B).

Of 22 patients, 16 (73%) achieved CR/ CR unconfirmed (CRu), three had progressive Disease (PD), and three were not Evaluable (NE) (Table 1). The first patient died of organ failure after the first chemotherapy cycle, the second of pneumonia after the third cycle, and the last was removed after the first cycle due to bronchial pneumonia.

Diagnostic accuracy and effectiveness

Ten patients started treatment based on clinical criteria alone; eight were later confirmed with IVL by pathological examination, giving an 80% concordance rate. The remaining two were diagnosed with DEN-

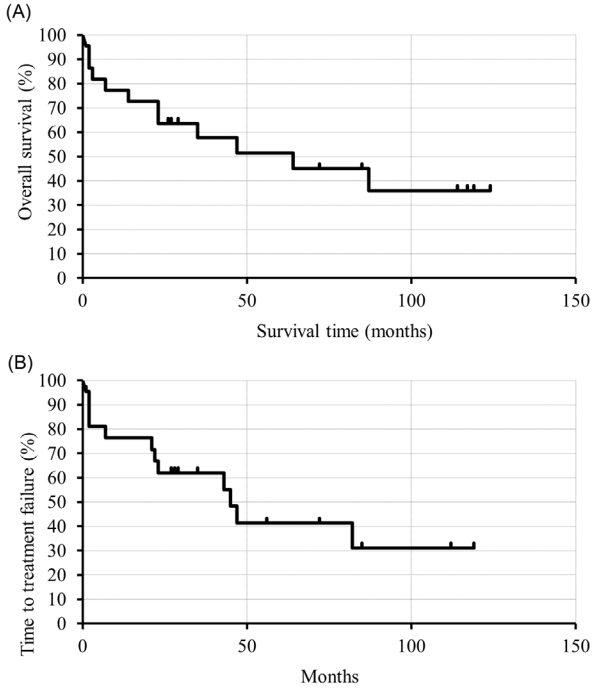

Figure 1. (A) Overall survival. The median overall survival (OS) was 65 months (11 deaths). Of these, five died during treatment without achieving complete response (CR). The causes of death included pneumonia (1), sepsis (1), multiple organ failure (2), and disease progression (1). Four patients died after recurrence, and two died while in remission of complications (one from cerebral infarction and the other from pneumonia). **(B) Time to treatment failure.** The median time to treatment failure (TTF) was 46 months, with six patients having recurrence. Of these, two patients received salvage treatment and were alive at the time of the last follow-up.

Table 1. Response

	All *n* = 22	R-CHOP *n* = 15	PBSCT+ *n* = 4	MTX+ *n* = 3
CR/Cru	16	9	4	3
PD	3	3	-	-
NE	3	3	-	-
Relapse	6	4	1	1

R-CHOP: R-CHOP therapy only. PBSCT+: Six cycles of R-CHOP, followed by PBSCT. MTX+: Six cycles of R-CHOP, followed by two cycles of high-dose MTX (2 g/m^2 as a single dose) and R-CHOP. CR: complete response, CRu: unconfirmed, PD: progressive disease, NE: not evaluable.

LBCL/IVL by BM smears, with monoclonal B-cell populations detected by flow cytometry.

BM examination diagnosed 14 (64%) of 22 patients with DEN-LBCL/IVL. RSB biopsy confirmed six (35%) of 17 patients. Three patients showed no lymphoma cells in BM or skin (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*).

Discussion

Most studies on IVL have examined a limited number of cases, often retrospectively, focusing on preexisting patient data. The standard treatment for IVL remains unestablished, with R-CHOP chemotherapy being the most administered regimen. A Japanese retrospective study (*11*) on 49 IVL patients treated with rituximab-containing chemotherapy reported an 82% CR rate, with progression-free survival (PFS) and OS rates at 2 years of 56% and 66%, respectively, aligning with outcomes in high-risk DLBCL patients classified by the IPI. In North America, a study (*12*) of 29 IVL patients revealed that 18 underwent first-line chemotherapy, with 15 completing it. Of those, 53% achieved CR, and the overall three-year survival rate was 42.7%, with a 64.2% event-free survival rate. In a retrospective study (*13*) of 12 patients with IVL conducted in China, 11 received R-CHOP therapy, and the overall response rate (ORR) and CR rate were 90.1% and 66.7%, respectively.

In the present study, the CR/CRu rate was 73%, with median OS and TTF of 65 and 46 months, respectively. To mitigate infusion reactions and severe BM suppression during the first chemotherapy cycle, a new regimen of dose-reduced CHOP (two-thirds of the normal dose) with delayed rituximab administration was used. The CR rate, OS, and TTF achieved were similar to those reported in previous studies (Supplemental Table S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Evaluations of high-dose chemotherapy combined with autoPBSCT in IVL patients are also limited to retrospective analyses. Meissner *et al.* (*14*) conducted a study on 11 IVL patients registered in the European Society for Blood and Marrow Transplantation database, treated with autoPBSCT. They reported two-year PFS and OS rates of 81% and 91%, respectively. Similarly, Kato *et al.* (*16*) retrospectively analyzed 61 IVL patients treated with autoPBSCT, reporting three-year OS and PFS rates of 89.1% and 82.8%, respectively.

In our study, four patients underwent high-dose chemotherapy with autoPBSCT. One patient experienced recurrence, but the others remained alive without recurrence at the time of analysis, with TTFs of 35, 43, 112, and 119 months, respectively. Three elderly patients ineligible for autoPBSCT received additional chemotherapy, including high-dose MTX. One had a recurrence in the BM, one died in remission from cerebral infarction, and the third was alive without recurrence at analysis.

Next, we assessed the concordance rate between clinical and pathological diagnoses in patients diagnosed using clinical criteria alone (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Of the 22 patients in the clinical trial, 10 started treatment based solely on these criteria. Eight were later definitively diagnosed with IVL *via* pathological examination, resulting in an 80% diagnostic concordance rate, which is satisfactorily high. Given the rapid progression of DEN-LBCL/IVL, patients often become too advanced for successful

treatment while awaiting a pathological diagnosis. The clinical diagnostic criteria used in this study are thus highly beneficial but do not always ensure an accurate diagnosis. Close monitoring and assessment are crucial when initiating treatment without a pathological diagnosis. Patients should be well-informed about their diagnosis and treatment. Ideally, treatment should commence after a definitive pathological diagnosis.

The diagnostic yields of BM examination and RSB were also evaluated. BM examination identified 14 patients with DEN-LBCL/IVL (64%). RSB were performed on 17 patients, detecting IVL in six (35%). Only three patients showed no infiltration in the BM or skin. Two of these were definitively diagnosed with IVL in other organs (spleen and brain). The last patient only had a clinical diagnosis of DEN-LBCL/IVL. RSB should be performed on all eligible patients as it is minimally invasive. Matsue *et al.* (*6*) reported a 71% positivity rate in RSB. In a study conducted by Maekawa *et al.* (*17*) in nine patients with IVL, they found significant detection rates of tumor cells in various skin layers, suggesting random skin biopsy using a 4-mm punch is effective for patients with thrombocytopenia and coagulation abnormalities. In the present study, only two patients were diagnosed with IVL by skin biopsy alone. However, because this procedure is minimally invasive, it should be performed on all eligible patients.

Shimada *et al.* (*18*) conducted a multicenter, prospective study on a chemoimmunotherapy regimen of R-CHOP followed by rituximab with high-dose MTX and additional R-CHOP cycles. The study showed this regimen's effectiveness in treating IVL patients. However, the included cases had relatively favorable conditions, with better PS and organ function. In practice, many IVL cases are severe and life-threatening; thus, after rapid BM and skin biopsy examination, chemotherapy may need to start before a definitive pathological diagnosis if the patient's PS deteriorates. Respecting Shimada's data, we conducted this trial for more severe cases. Early treatment based on clinical diagnostic criteria could save many DEN-LBCL/IVL patients, especially those of advanced age or with multiple organ failure.

Our study had several limitations. First, the case enrollment period was very long, spanning 10 years, with only 22 patients registered, averaging just 2.2 cases per year. Second, due to the long enrollment period, the observation period varied greatly according to the date of registration; however, the survival curves did not reach the plateau phase in both OS and TTF.

In conclusion, patients with DEN-LBCL, including IVL, were effectively treated with a new chemoimmunotherapy regimen starting with dose-reduced CHOP and delayed rituximab, followed by conventional R-CHOP. The clinical diagnostic criteria were helpful for early intervention. Larger studies are needed to confirm these findings.

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