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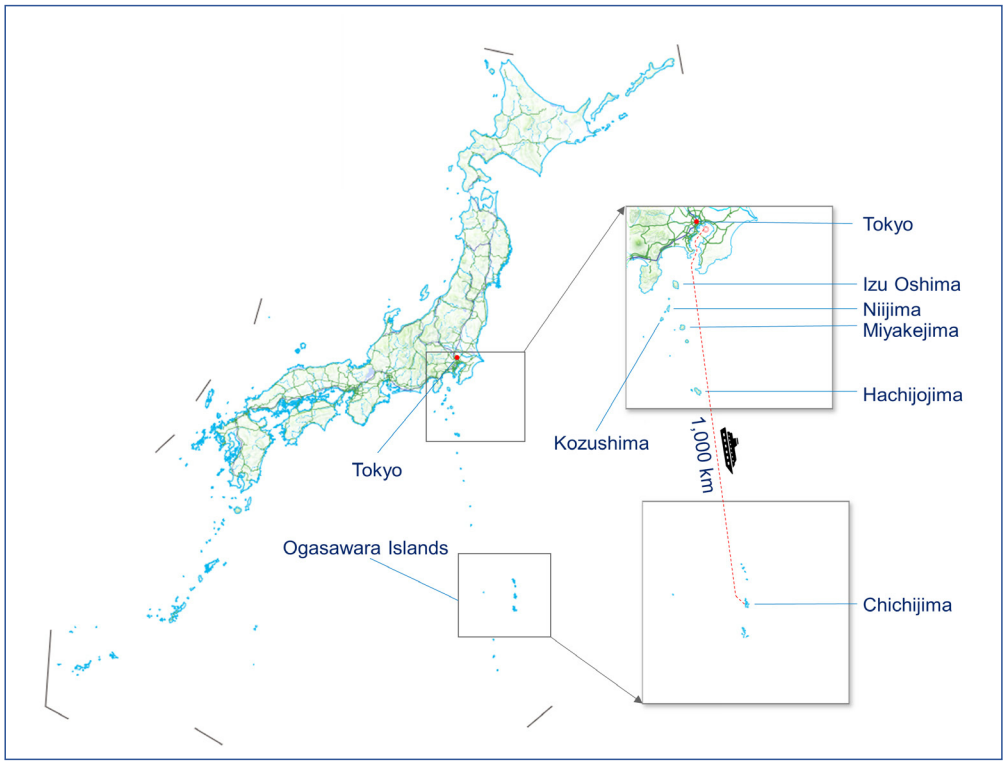

PCR testing prior to ship boarding to prevent the spread of SARS-CoV-2 from urban areas to less-populated remote islands (Page 175)

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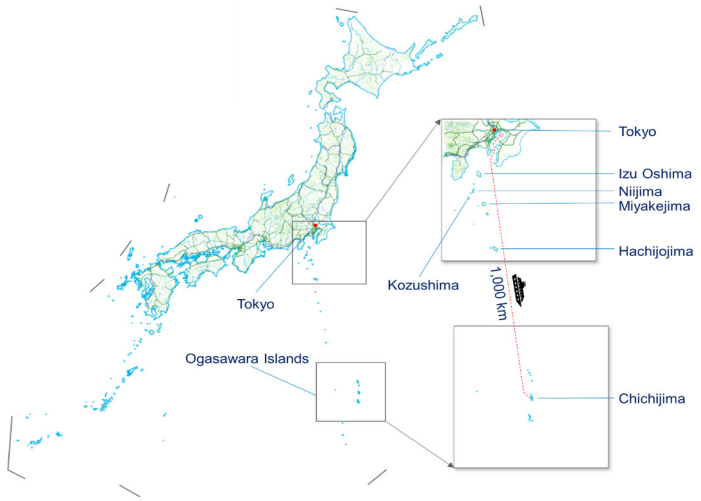

Chichijima is the largest island in the Ogasawara Islands, located about 1,000 km south of Tokyo and inhabited by approximately 2,100 residents. The only way to reach Chichijima is by ship, taking approximately 24 h from Tokyo. The island is with limited medical system and SARS-CoV-2 screening has been conducted so that infected individuals are prevented from reaching the island (Page 175).

Global Health & Medicine. 2022; 4(3):146-151. ORIGINAL ARTICLE

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Possible association of *HLA-DP* polymorphism and antiretroviral therapy with hepatitis B virus clearance in an HIV-infected Vietnamese population

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Abstract: There is little evidence regarding the association between hepatitis B virus (HBV) chronicity and *HLA-DP* among the HIV-infected Vietnamese population. To study this, we conducted a cross-sectional analysis and a prospective study involving an HIV-infected Vietnamese cohort. The association between HBV chronicity and *HLA-DP* single nucleotide polymorphisms (SNPs) of rs3077 and rs9277535 among Vietnamese patients with previous HBV exposure was first evaluated. In addition, treatment-naive patients with chronic HBV infection were followed between 2012 and 2017 for HBV clearance after the initiation of antiretroviral therapy (ART). A total of 820 subjects with previous HBV exposure were included in the cross-sectional study. Among them, 147 (17.9 %) had chronic HBV infection, and 673 (82.1 %) achieved HBV clearance. The proportions of minor allele homozygotes of rs3077 and rs9277535 were 10.9 % and 15.2 % (p = 0.481) and 4.1 % and 11.7 % (p = 0.003), respectively. Multivariate analysis showed that rs9277535 minor homozygote was a significant protective factor against chronic HBV infection (odds ratio [OR], 0.271; 95 % confidence interval [CI]; 0.114-0.642, p = 0.001). Further, none of the 43 patients in the prospective study, who received ART possessed the rs9277535 minor homozygote. The average follow-up period was 4.8 years, and 10 subjects (23.3 %, 4.9 %/person-years) achieved HBV clearance. Univariate analysis revealed that the SNPs were not significantly associated with HBV clearance. In conclusion, our study confirmed that the rs9277535 minor allele homozygote was significantly associated with HBV clearance among HIV-infected Vietnamese patients.

***Keywords*:** hepatitis B virus, HIV, *HLA-DP*, Vietnamese

Introduction

Hepatitis B virus (HBV) infection is a global public health threat, with more than 240 million carriers worldwide (*1*). Chronic HBV infection (*i.e.*, positive for hepatitis B surface antigen [HBsAg] for at least six months) is highly endemic in Asia, where its prevalence is more than 8 % in some countries (*2*). The estimated prevalence of chronic HBV infection in Vietnam is over 8 % in the general adult population (*1*) and reaches up to 15 % in people who use drugs or female sex workers (*3*). More than 70 % of new hepatocellular carcinomas (HCCs) diagnosed globally were reported from Asia, where chronic HBV infection is one of the major causes of HCC (*4*).

Although the mechanisms that contribute to HBV chronicity and clearance are not fully understood, various factors including those related to the virus and host and other extrinsic elements are considered important. Considering host-related factors, age at which infection occurred was strongly and inversely related to the risk of chronicity. Ninety percent of perinatally acquired HBV infections develop into chronic HBV infections (*5*); 20-50% of children between the age of one and five years old (*6*), and less than 5% of adults develop chronic HBV infections (*7*). Previous genome-wide association studies (GWAS) identified relationships between *HLA-DP/DQ* polymorphisms (*HLA-DP* rs3077, rs9277535, *HLA-DQ* rs2856718, rs7453920) and HBV clearance (*8,9*). These findings were confirmed among various ethnic groups, including the Japanese, Han Chinese, Korean, Thai, and Saudi Arabian populations (*10-12*).

Additionally, HBV and HIV infections are commonly diagnosed in the same patient because both these viruses share similar routes of transmission. Unlike HBV mono-infected patients, all HIV/HBV co-infected patients should be treated to suppress both viruses regardless of HBV DNA level or degree of liver damage (*13*).

The preferred regimen for HIV infection includes a combination of lamivudine (3TC) or emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), which acts strongly against HBV. These therapies suppress HBV and HIV viral loads and prevent the development of hepatic complications (*14*); however, HBsAg antigen clearance is rarely achieved. The relationship between HBsAg clearance and *HLA-DP* single nucleotide polymorphisms (SNPs) among people living with HIV remains to be elucidated. Thus, we evaluated the relationship between HLA and HBsAg clearance among a Vietnamese population living with HIV in a cross-sectional study. Further, we evaluated the relationship between HLA and response to treatment using a TDF/3TC-based regimen in a longitudinal study in Vietnam.

Patients and Methods

Study design

We performed a cross-sectional study and a prospective, observational study on a single-center cohort of Vietnamese HIV-infected individuals to evaluate the relationship between *HLA-DP* SNPs and HBsAg clearance. This cohort was established in 2007 at the National Hospital for Tropical Disease (NHTD) in Hanoi, one of the largest outpatient clinics for HIV-infected patients in Vietnam. The population of this cohort comprised Vietnamese HIV-infected patients aged > 18 years who were referred to the NHTD.

In the cross-sectional study, to analyze the relationship between *HLA-DP* and HBsAg clearance, all the participants enrolled in the cohort until May 2016 were evaluated for their HBV status, including HBsAg, hepatitis B surface antibody (HBsAb), hepatitis core antigen (HBcAg), and hepatitis C antibody (HCVAb) at the time of recruitment. Those who tested positive for HBcAb were regarded as subjects with previous HBV exposure and were included in the present study. These subjects were evaluated for their *HLA-DP* and other factors including liver enzyme, administration of antiretroviral therapy (ART), and immune status to analyze the relationship between HBV chronicity and factors including *HLA-DQ*.

In the prospective study, ART-naive subjects with chronic HBV infection were included and followed for HBV clearance after initiation of ART between October 2012 and October 2019. In addition to the testing of factors mentioned in the cross-sectional study, HBe antigen (HBeAg) and HBV DNA were measured every six months; HBV genotype and HBV drug resistance were measured at baseline. The association between HBV clearance, antiretroviral treatment, and other factors, including *HLA-DP*, were prospectively evaluated. The definition of HBV clearance was defined as HBs Ag conversion from positive to negative, namely, HBs Ag clearance.

Measurements

Clinical and laboratory data included demographic variables (age and sex), history of ART, CD4+ cell count (cell/mm^3, measured by flow cytometry), plasma HIV RNA (copies/mL, measured by the Roche COBAS TaqMan HIV monitor assay), serum aspartate aminotransferase (AST, U/L), and alanine aminotransferase (ALT, U/L). As serological markers of HBV, HBsAg (IU/mL) and HBeAg (signal to cut-off ratio, S/CO) were measured using a chemiluminescent enzyme immunoassay (CELIA). HBV DNA was measured using real-time polymerase chain reaction (PCR). For the genotyping assay of HBV, eight genotypes (A to H) were determined genetically using the PCR-invader method (structure-specific 5' nuclease-based method). To evaluate *HLA-DP* SNPs, two SNPs at the 3' untranslated region of *HLA-DPA1* and *HLA-DPB1* gene, namely, rs3077 and rs9277535 were selected because in previous studies these SNPs were identified as having a strong correlation with HBV chronicity (*8,15*). TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, MA, USA) were used to determine the rs3077 and rs9277535 genotypes.

Statistical analysis

In the cross-sectional study, characteristics were compared between HBsAg-positive and HBsAg-negative patient groups using the Student's *t*-test for continuous variables and either the χ^2 test or Fisher's exact test for categorical variables. In the prospective study, the time from baseline to HBV clearance was analyzed using Cox proportional hazards regression analysis to estimate the impact of *HLA-DP* SNPs and other factors on the incidence of HBV clearance. Variables significantly associated with HBsAg clearance in the univariate analysis ($p < 0.05$) were entered into the multivariate analysis. Statistical significance was defined as a two-sided p value < 0.05. All statistical analyses were performed using SPSS software, version 23.0 (IBM Corp., Armonk, N.Y., USA).

The study was approved by the Human Research Ethics Committee of NCGM (NCGM-A-000238-00) and NHTD (IORG 0006480). All the study participants provided written informed consent for the use and publication of their clinical and laboratory data. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Since October 2007, 1,820 patients were registered for the cohort; 1,441 were enrolled and underwent follow-up in May 2016. Of them, 820 were positive for HBcAb and

were included in the cross-sectional study. Table 1 shows the basic demographics of patients with and without HBsAg positivity at the time of enrollment. Of the 820 study subjects, 147 (17.9%) had chronic HBV infection, and 673 (82.1%) achieved HBV clearance. The average age of patients with and without chronic HBV infection was 34.5 and 35.2 years, respectively (p = 0.343). The proportion of females was 28.5% and 31.6% in both these groups, respectively (p = 0.223). The average serum AST and ALT levels in these groups were 36.6 and 41.0 U/L (p = 0.099) and 42.4 and 47.1 U/L (p = 0.192), respectively. The average CD4+ cell count, indicating HIV infection status of these groups was 277.3 and 263.5 (cell/mm^3), respectively. The proportion of patients with HIV RNA < 200 copies/mL and the proportion of patients who underwent ART in the two groups were 68.7 % and 73.0 % (p = 0.391) and 78.2 % and 84.8 % (p = 0.049), respectively. The proportion of patients positive for HCVAb was 42.1 % and 27.3 % (p = 0.254), respectively. *HLA-DP* polymorphism signified by the proportions of minor allele homozygotes of rs3077 (AA) and rs9277535 (AA) were 10.9% and 15.2% (p = 0.481) and 4.1% and 11.7% (p = 0.003), respectively.

In univariate analysis, SNP rs9277535 was significantly associated with HBsAg clearance and the administration of ART and SNP rs3077 was marginally associated with HBsAg clearance (Table 2). These three factors were entered into the multivariate analysis and the rs9277535 minor homozygote was identified as a significant protective factor against chronic HBV infection (odds ratio [OR]: 0.271, 95 % confidence interval [CI]; 0.114-0.642, p = 0.001), and the administration of ART was marginally associated with HBsAg clearance (OR, 0.646; 95 % CI, 0.411-1.014; p = 0.057).

A prospective study was also conducted to evaluate HBsAg clearance followed by HIV/HBV treatment with TDF/3TC among treatment-naive patients with HIV and chronic HBV coinfection. During the study period, 43 patients were included in this prospective study, and ART was initiated. Baseline characteristics are shown in Table 3. The mean age was 34.7 years, and 32.6% (14/43) were women. While 42 of the patients (97.7%) were administered ART containing TDF/3TC, the remaining

Table 1. Baseline characteristics of Vietnamese patients according to HBsAg status in the cross-sectional study

Variables	Overall (n = 820)	HBsAg Positive (n = 147)	HBsAg Negative (n = 673)	p value
Age, years	35.1 ± 8.56	34.5 ± 7.79	35.2 ± 8.71	0.343
Female, n (%)	252 (30.7)	39 (26.5)	213 (31.6)	0.223
HCVAb (+), n (%)*	360 (46.3)	61 (42.1)	299 (47.3)	0.254
Asparate aminotransferase, U/L	41.0 ± 35.0	36.6 ± 20.5	41.9 ± 37.3	0.099
Alanine aminotransferase, U/L	46.3 ± 40.2	42.4 ± 28.3	47.1 ± 42.4	0.192
CD4+ cell count, cell/μL	266.0 ± 176.0	277.3 ± 170.7	263.5 ± 177.1	0.391
HIV RNA < 200 copies/ml, n (%)	592 (72.2)	101 (68.7)	491 (73.0)	0.298
Use of ART, n (%)	686 (83.7)	115 (78.2)	571 (84.8)	0.049
SNPs (rs3077) minor allele homozygote, n (%)	118 (14.4)	16 (10.9)	102 (15.2)	0.481
SNPs (rs3077) heterozygote	325 (39.6)	53 (36.0)	272 (40.4)	0.327
SNPs (rs3077) major allele homozygote, n (%)	377 (46.0)	78 (53.1)	299 (44.4)	0.057
SNPs (rs9277535) minor allele homozygote, n (%)	85 (10.4)	6 (4.1)	79 (11.7)	0.003
SNPs (rs9277535) heterozygote, n (%)	338 (41.2)	54 (36.7)	284 (42.2)	0.223
SNPs (rs9277535) major allele homozygote, n (%)	397 (48.4)	87 (59.2)	310 (46.1)	0.004

Data are expressed as mean ± SD or n (%). HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ART, antiretroviral therapy; SNP, single nucleotide polymorphism. *There are missing values.

Table 2. Evaluation of factors associated with HBsAg clearance using univariate and multivariate analyses

Variables	Univariate analysis		Multivariate analysis		
	OR	95% CI	OR	95% CI	p value
Age	0.990	0.968 – 1.011			
Female sex	0.780	0.522 – 1.164			
HCVAb (+), n (%)*	0.809	0.562 – 1.165			
Asparate aminotransferase, U/L	1.001	0.998 – 1.004			
Alanine aminotransferase, U/L	1.000	0.998 – 1.003			
CD4+ cell count, cell/μL	1.000	0.999 – 1.001			
HIV RNA < 50 copies/mL, n (%)	0.814	0.552 – 1.200			
Administration of ART	0.642	0.411 – 1.002	0.646	0.411 – 1.014	0.057
SNPs (rs3077) minor allele homozygote	0.601	0.336 – 1.077	0.889	0.467 – 1.690	0.719
SNPs (rs9277535) minor allele homozygote	0.271	0.114 – 0.642	0.296	0.118 – 0.743	0.010

OR, odds ratio; CI, confidence interval HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ART, antiretroviral therapy; SNP, single nucleotide polymorphism. *There are missing values.

one subject received ART containing only 3TC as an effective agent against HBV. Ten (23.3 %) subjects were positive for HBeAg. HBV DNA was undetectable in nine (20.9%) patients. Among the 35 subjects with successful genotype analysis, genotype B was the most prevalent (29/35, 23 for genotype Ba and two for genotype B, subtype not determined), followed by genotype C (7/35). HBV resistance to entecavir was observed in 6.5% (2/31) of the patients. Twelve (27.9%) subjects were HCV-positive. None of them possessed the *HLA-DP* rs9277535 minor homozygote, which was identified as a protective factor for chronic HBV infection in the cross-sectional study. The *HLA-DP* rs3077 minor allele homozygote was observed in four (9.3%) subjects.

Table 3. Baseline characteristics of treatment-naive HIV-infected Vietnamese patients in the prospective study

Variables	Overall (*n* = 43)
Age, years	34.7 ± 9.6
Female, *n* (%)	14 (32.6)
HCVAb (+), *n* (%)*	12 (27.9)
Asparate aminotransferase, U/L	41.2 ± 21.6
Alanine aminotransferase, U/L	39.0 ± 23.1
CD4+ cell count, cell/μL	280.2 ± 161.6
HIV RNA load, copies/mL	143,593.6 ± 327,525.7
HBsAg,	5,503 ± 13,015.9
HBeAg positive, *n* (%)	10 (23.3%)
HBV DNA	4.5 ± 3.2
HBV genotype, *n* (%)*	Genotype B, 29 (82.9) Genotype C, 7 (20) Mix of B and C, 1 (2.9)
HBV drug resistance, *n* (%)*	2 (6.5)
SNPs (rs3077)	
Minor allele homozygote	3 (7.0)
Heterozygote	21 (48.8)
Major allele homozygote	19 (44.2)
SNPs (rs9277535)	
Minor allele homozygote	0 (0)
Heterozygote	18 (41.9)
Major allele homozygote	25 (58.1)

Data are expressed as mean ± SD or *n* (%). HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis E surface antigen; SNPs, single nucleotide polymorphisms. *There are missing values.

These 43 subjects were followed until October 2019 (average follow-up period 4.8 years). Of them, 10 (23.3%, 4.9%/person-years) achieved HBsAg clearance. Of 10 with HBeAg positive at the baseline, among whom one (10%, 1.94%/person-years) subject achieved HBeAg clearance. Although the sample size was quite limited, we attempted to identify factors associated with HBsAg clearance, including *HLA-DP* (Table 4). In univariate analysis, the SNPs were not significantly associated with HBsAg clearance, while the inverse association of HBV DNA with HBsAg clearance was statistically significant.

Discussion

In our cross-sectional study, we found that HBV clearance was associated not only with *HLA-DP* rs9277535 minor homozygote, but also with ART among HIV-infected Vietnamese patients. To the best of our knowledge, this is the first study to illustrate these associations among HIV-infected Vietnamese individuals. However, our attempt to elucidate the causative relationship between HBV clearance and *HLA-DP* among the HIV-infected Vietnamese patients who received ART in the prospective study was unsuccessful. This was because these subjects did not possess the *HLA-DP* rs9277535 minor homozygote, probably on account of the allele's protective nature against HBV chronicity. Our cross-sectional and prospective studies showed that there was no relationship between rs3077 minor allele homozygote and HBV clearance; this finding corresponds to that of a previous study conducted in Taiwan (*16*). Although it may be roughly speculated that the irrelevance of rs3077 could be because of the

Table 4. Factors associated with HBsAg clearance in the prospective study estimated by univariate analysis

Variables	Univariate analysis		
	HR	95% CI	*p* value
Age, years	1.002	0.940 – 1.068	0.958
Female, *n* (%)	0.772	0.199 – 2.998	0.709
HCVAb (+)*	0.685	0.142 – 3.309	0.638
Asparate aminotransferase, U/L	0.962	0.916 – 1.009	0.112
Alanine aminotransferase, U/L	0.976	0.936 – 1.018	0.253
CD4+ cell count, cell/μL	1.001	0.997 – 1.006	0.587
HIV RNA load, copies/mL	1.000	1.000 – 1.000	0.840
HBsAg	1.000	0.999 – 1.000	0.162
HBeAg positive	0.030	0.000 – 10.885	0.243
HBV DNA	0.764	0.616 – 0.949	0.015
HBV genotype#	0.027	0.000 – 231.5	0.435
HBV drug resistance#	1.000	0.000 – 46,237.8	1.000
SNPs (rs3077) minor allele homozygote	0.046	0.000 – 1,132,461.3	0.723
SNPs (rs9277535) heterozygote	0.271	0.034 – 2.172	0.219

#10 patients cleared HBsAg after initiation of ART among 43 patients with chronic HBV infection in this prospective phase (see Table 3). HR, hazard ratio; CI, confidence interval HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis E surface antigen; SNPs, single nucleotide polymorphisms; ART, antiretroviral therapy. *There are missing values.

Vietnamese ethnicity of the study group, considering the relatively close ethnicity between our study group and that of the Taiwanese study group, further research is warranted.

Previous study findings show that the rate of HBsAg clearance after initiation of different therapeutic strategies among HIV/HBV co-infected individuals varied between 1.7% and 2.6%/person-years; this was lower than the value of 4.9%/person-years determined in the current study (*17-19*). This result may be attributed to the relatively longer follow-up period in our study. In addition to TDF containing ART, higher CD4+ T cell counts have been identified in previous studies (*20,21*). Our findings in the prospective study indicate that no factors are associated with HBsAg clearance; this may be attributed to the small sample size. Nevertheless, a recent study revealed that immune reconstitution-induced inflammatory syndrome (IRIS) after ART was associated with HBsAg loss in HIV/HBV co-infected individuals (22). Although IRIS was not assessed in our study, the relationship between IRIS and *HLA-DP* is of interest and requires further investigation, given the hypothesis that IRIS is induced by HBV-specific cytotoxic CD8+ T cells, which could be related to *HLA-DP*. The study lacked subjects with rs9277535 minor allele, one of the key factors, in the prospective study, resulting in inability to evaluate exact impact of *HLA-DP* on HBsAg clearance. Further prospective studies with larger sample size are required for sound analysis, given a possible protective effect of this factor on HBV clearance.

This study has several limitations. First, the time and mode of HBV transmission were unknown in most cases in this study; thereby, resulting in difficulty in estimating whether HBsAg clearance was achieved before or after acquisition of HIV among the subjects who tested negative for HBsAg and positive for HBcAb. This information would have been especially useful in the cross-sectional study where 83.7% of the participants received ART at the time of enrollment into the cohort. However, the finding in the cross-sectional study that identified ART as a factor associated with HBsAg clearance suggest that most subjects achieved HBsAg clearance after HIV acquisition. Second, while we evaluated the association of only two *HLA-DP* SNPs, *i.e.*, rs3077 and rs9277535 with HBV clearance, more recent studies analyzed multiple HLA polymorphism alleles using a GWAS. This might have been one of the causes for negative outcomes in the prospective study, in addition to the small sample size and the absence of *HLA-DP* rs9277535 minor homozygote in the subjects, which was the main focus of the study; this precludes a sound analysis such as Mendelian randomization. The impact of HLP-DP genotypes on HBV clearance in this special population needs to be evaluated in a further study.

In conclusion, the present study showed that the *HLA-DP* minor allele rs9277535 homozygote and ART were significantly and marginally associated with HBsAg clearance, respectively, among HIV-infected Vietnamese individuals in the cross-sectional study. Nevertheless, further prospective studies with larger sample size are warranted to confirm the causative relationship.

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Conflict of Interest: S.O. has received research grants from ViiV Healthcare and Gilead Sciences, and honoraria for lectures from MSD K.K., ViiV Healthcare, and Gilead Sciences. H.G. received honoraria from MSD K.K., Abbott Japan, Co., Janssen Pharmaceutical K.K., Torii Pharmaceutical, Co., Roche Diagnostics K.K., and ViiV Healthcare, Co. The sponsors had no role in study design, collection, analysis and interpretation of data, article writing and publication decisions. The remaining authors have no conflicts of interest to disclose.

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The importance of an eating disorder treatment support center in Japan: A survey from 2017 to 2020

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Abstract: We investigated the impact of medical collaboration between the Chiba Eating Disorder (ED) Treatment Support Center (CSC) in Chiba Prefecture and the ED treatment center at Kohnodai Hospital. We calculated the number of consultations performed by the CSC and referral rate to other medical facilities from October 2017 to March 2020, as well as the clinical characteristics of the patients treated at our hospital from April 2016 to March 2020. Data on duration of hospitalization and increase in body mass index (BMI) during hospitalization were recorded. Patients were divided into all of the Japan and Chiba Prefecture groups. Data were evaluated by Poisson's regression analysis or one-way analysis of variance. A p-value < 0.05 was considered significant. The 2019 data served as reference values. Our data demonstrated that while the number of CSC consultations increased (2017:201, 2018:547, 2019:552) annually, the number of hospitalizations for EDs decreased (197, 194, 134, respectively). In comparison, the number of outpatient consultations for EDs across all of Japan peaked in 2018 and decreased significantly thereafter (2016:110, 2017:139, 2018:193, 2019:142). After the CSC was established, the number of patients treated in our department decreased as expected. Patients with anorexia nervosa (AN) who were treated on an outpatient basis across all of Japan were younger in 2019 (27.0 ± 1.2) than in 2018 (31.9 ± 1.2). Severe cases had better outcomes, and there was a significant increase in BMI of inpatients with AN in both groups. Overall, the activities of such ED treatment support center promoted successful treatment of severe ED cases.

***Keywords*:** eating disorder, anorexia nervosa, medical collaboration, support center

Introduction

Eating disorders (EDs) are serious psychiatric conditions characterized by abnormal eating or weight-control behaviors (*1,2*). The main EDs subcategories include anorexia nervosa (AN), which is characterized by a bodyweight below the lower limit of normal based on age and height, and bulimia nervosa (BN), which is characterized by a bodyweight within the normal range. The other subcategories under EDs include binge-eating disorder, other specified feeding and eating disorders, and avoidant/restrictive food intake disorders. In the studies in English or French published between 2000 and 2018, the weighted mean (ranges) of the lifetime of EDs were 8.4% (3.3-18.6%) for women and 2.2% (0.8-6.5%) for men (*3*). A meta-analysis estimated that mortality rate of AN over 10 years was approximately 5-6%, which is high compared with other psychiatric disorders (*1-4*). The 5-year clinical recovery rate was reportedly 66.8% (*5*). The causes of death in AN include arrhythmia, infectious disease from extreme malnutrition, and suicide (*6,7*). Because of the potentially fatal complications of AN, a combination of medical treatment and psychotherapy is necessary. In 2009, the Mental and Disability Health Division of the Ministry of Mental Health and Welfare of Japan recorded 210,000 receipt claims for outpatient and inpatient treatment of EDs (*8*).

Unfortunately, Japan lacks independent specialized treatment facilities for EDs. Psychiatric hospitals and clinics without internal medicine departments, as well as a small number of general hospitals, are mainly responsible for providing ED treatment; however, many doctors in general hospitals lack training to treat these diseases. As a result, patients with severe malnutrition have difficulty getting adequate treatment. Many facilities are also concerned that publicity will result in an unmanageable number of patients with EDs. Ensuring cooperation between medical and psychiatric departments is a key issue in Japan. There are negative

stereotypes and prejudices (*e.g.*, weakness, laziness, carelessness) about ED among the general public and healthcare professionals, which have a negative impact on treatment desires (*9*).

To solve these problems, the government established four ED treatment support centers (Tohoku University Hospital in Miyagi Prefecture, Kohnodai Hospital of the National Center for Global Health and Medicine in Chiba Prefecture, Hamamatsu University Hospital in Shizuoka Prefecture, and Kyushu University Hospital in Fukuoka Prefecture) (*10*). These centers: *i*) provide medical care information for patients and their families, *ii*) educate therapists and train doctors from other medical institutions, and *iii*) promote medical cooperation. The National Center of Neurology and Psychiatry was designated as the National Core Center for Eating Disorders. It holds domestic meetings and collates the findings from each center (*11*).

Despite the presence of these programs, patients still have difficulty finding an institution that provides adequate treatment. To improve this situation, we investigated the change in clinical status of patients who visited Kohnodai Hospital after establishment of our treatment center.

We hypothesized that the Chiba Eating Disorder Treatment Support Center (CSC) would encourage cooperation between psychiatry and internal medicine physicians treating patients with EDs and solve the above problems. We also theorized that establishing a center would increase the number of treatment facilities for patients with EDs in Chiba and other prefectures. Patients will be able to visit the hospital more easily than before. Specialized treatment hospitals would lead to a gradual decrease in the total number of inpatients and concentrate specialized treatment for the most severely ill patients.

Materials and Methods

Study design and Data collection

We recorded the number and type of consultations done by the CSC and the percentage of patients who were subsequently referred to our ED treatment center at Kohnodai Hospital for three years from October 2017 to March 2020 ((1) 2017.10-2018.3, (2) 2018.4-2019.3, (3) 2019.4-2020.3) (Figure 1). We also surveyed the number of patients who received outpatient or inpatient treatment at Kohnodai Hospital over a 4-year period from April 2016, before the CSC was established, until March 2020 (① 2016.4-2017.3, ② 2017.4-2018.3, ③ 2018.4-2019.3, ④ 2019.4-2020.3) (Figure 1). We recorded the data of patients who received outpatient or inpatient treatment at Kohnodai Hospital from one year prior to the opening of the CSC to show the effectiveness of the CSC activities more clearly.

For inpatients, we investigated the duration of hospitalization and body mass index (BMI) at the time of hospitalization and discharge. Patients who were treated for two weeks or less were excluded from this study because we could not adequately assess their weight gain over this duration. The data of patients from the Chiba prefecture and all of Japan, including Chiba residents, were analyzed separately.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, whereas categorical variables were expressed as numbers and percentages. To assess the differences in the number of consultations conducted by the CSC annually, a Poisson regression analysis was performed, where the number of consultations was defined as the dependent variable. A dummy variable corresponding to the year was used as the independent variable, and the year 2019 was used as the baseline for all dummy variables. The same Poisson regression analysis was performed for inpatients and outpatients with EDs and AN, respectively.

A one-way analysis of variance was performed to compare the age, duration of illness, BMI at admission and discharge, and increase in BMI during hospitalization for each year. If the effect of the year was significant, pairwise comparisons were performed using the Dunnett method with the year 2019 used as the baseline. The normality and homogeneity of

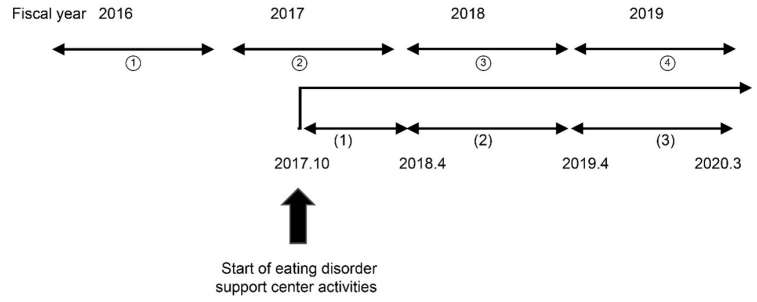

Figure 1. Research protocol. The horizontal axis shows the fiscal year and the date. The start of the support center is indicated by a vertical arrow. Data on hospital patients were collected one year before the start of Chiba Eating Disorder Support Treatment Center.

variance of the analyzed data were established.

All statistical analyses were conducted with SPSS version 26 (SPSS, Armonk, NY, USA). All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. This study was approved by the Ethics Committee of Kohnodai Hospital (NCGM-G-003196-00, NCGM-G-003071-00). All patients provided informed consent.

Results

The total consultations in the CSC in 2017, 2018, and 2019 was 201, 547, and 552, respectively (Table 1). In comparison, the number of first-time consults during these periods numbered 129, 465, and 477, respectively. The proportions of the various people seeking consultation are shown in Table 1. The majority of the consults were conducted with the patients and their mothers. When a person requested information on the medical institutions that were appropriate for their individual needs, such information was carefully researched and presented by the staff. The total number of referrals to medical facilities, including Kohnodai Hospital, in 2017, 2018, and 2019 were 83, 402, and 586, respectively (Figure 2). The percentage of referrals made to Kohnodai Hospital decreased during the 3-year period. There were more referral facilities than the number of consultations because the medical cooperation system increased the number of referral options.

Change in the number of patients treated at Kohnodai Hospital

The number of outpatient medical examinations conducted for patients with an ED or AN and the basic data of the patients who came in for these examinations over the 4-year period are summarized in Table 2 and Figure 3. The data were evaluated by Poisson's regression model using the 2019 values as the baseline.

In the all-Japan group, the number of patients with EDs in 2019 (142 cases) was significantly different from that in 2016, 2017, and 2018 (110, p = 0.00; 139, p = 0.001; and 193, p = 0.003; respectively). Moreover, the number of patients peaked in 2018 and declined thereafter. In comparison, in the Chiba Prefecture group, the number of patients with EDs in 2019 was significantly lower than that in 2018 (89 *vs.* 123, p = 0.02). Among the patients with AN, the number of patients in the Chiba Prefecture (56 *vs.* 80, p = 0.022) and all Japan groups (93 *vs.* 127, p = 0.041) was significantly lower in 2019 than in 2018. In general, the number of outpatient examinations increased until 2018 and decreased thereafter.

The number of inpatients with EDs in the Chiba Prefecture and all Japan groups was significantly higher in 2016 (133: p = 0.000; 211: p = 0.000), 2017 (115: p = 0.003; 197: p = 0.001), and 2018 (126: p = 0.000; 194: p = 0.001) than in 2019 (74,134). The number of inpatients with AN in the Chiba Prefecture and all Japan groups was significantly higher in 2016 (105: p = 0.001; 171: p = 0.000), 2017 (96: p = 0.004; 169: p = 0.001), and 2018 (102: p = 0.001; 160: p = 0.003) than in 2019 (60, 111).

Age at the first visit, BMI at admission, and duration of hospitalization

The age and duration of illness (mean ± standard error) of the patients treated on an outpatient and inpatient basis are shown in Table 2 and Table 3, respectively. The factors that showed statistical significance in the one-way analysis of variance are summarized in Figure 3. There were no significant differences in the age or duration of disease between the all Japan and Chiba Prefecture groups for patients with ED (Table 2).

The age of the outpatients with AN in the all Japan group was significantly higher in 2018 than in 2019 (Table 2, p = 0.019). The BMI at admission among the inpatients with AN in the Chiba Prefecture group was significantly higher in 2018 than in 2019 (Table 3, p = 0.025). The inpatients with AN in the Chiba Prefecture group were hospitalized for a significantly shorter time in 2016 (p = 0.008), 2017 (p = 0.027), and 2018 (p = 0.030) than in 2019.

Table 1. Proportion of people seeking consultation in the Chiba Eating Disorder Treatment Support Center (CSC)

Person or affiliation (year)	2017	2018	2019
Total number	201	547	552
Patient (%)	32	29	33
Mother (%)	39	37	39
Father (%)	6	9	7
Husband/wife (%)	6	4	7
Administrative organization (%)	1	2	2
Educational institution (%)	2	1	1
Medical institution (%)	1	3	2
Other/unknown (%)	13	15	9

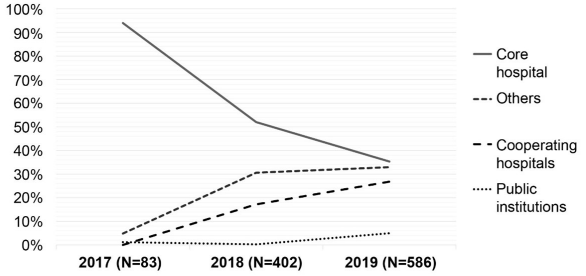

Figure 2. The total number of referrals to medical facilities, including Kohnodai Hospital, in 2017, 2018, and 2019 were 83, 402, and 586, respectively. Line graph shows the percentage of referrals made to Kohnodai Hospital decreased during the 3-year period. The referral rate to our hospital (Kohnodai Hospital) has been decreasing year by year.

Table 2. Basic data of ED and AN outpatients treated at Kohnodai Hospital

	2016	2017	2018	2019	*p*
Outpatient ED					
Number of patients					
All Japan group	110	139	193	142*	*vs.* 2016, 2017, 2018
Chiba Prefecture group	69	87	123	89*	*vs.* 2018
Age at first visit (years)					
All Japan group	28.3 ± 1.2	27.1 ± 0.9	29.9 ± 0.9	27.8 ± 0.9	n.p.
Chiba Prefecture group	27.7 ± 1.6	26.8 ± 1.2	29.9 ± 1.2	28.2 ± 1.2	n.p.
Duration of illness (days)					
All Japan group	3,384.9 ± 364.5	2,869.9 ± 254.7	3,217.2 ± 222.7	3,230.5 ± 277.8	n.p.
Chiba Prefecture group	3,183.6 ± 483	2,964.5 ± 331.4	3,327.9 ± 277.4	3,233.3 ± 363.4	n.p.
Outpatient AN					
Number of patients					
All Japan group	78	89	127	93*	*vs.* 2018
Chiba Prefecture group	47	54	80	56*	*vs.* 2018
Age at first visit (years)					
All Japan group	29.2 ± 1.5	28.4 ± 1.3	31.9 ± 1.2	27.0 ± 1.2*	*vs.* 2018
Chiba Prefecture group	29.1 ± 2.1	27.3 ± 1.6	31.8 ± 1.5	27.3 ± 1.7	n.p.
Duration of illness (days)					
All Japan group	3,554.1 ± 453.7	3,058.4 ± 345	3,556.5 ± 294.9	2,881.7 ± 337.5	n.p.
Chiba Prefecture group	3,485.4 ± 623.5	3,048.1 ± 459.3	3,721.5 ± 378.9	2,767.6 ± 435.7	n.p.
BMI at first visit (kg/m^2)					
All Japan group	14.1 ± 0.3	14.0 ± 0.3	14.5 ± 0.3	14.5 ± 0.3	n.p.
Chiba Prefecture group	14.0 ± 0.3	14.5 ± 0.4	14.7 ± 0.3	14.6 ± 0.4	n.p.

*p-value < 0.05. ED, eating disorders; AN, anorexia nervosa; BMI, body mass index.

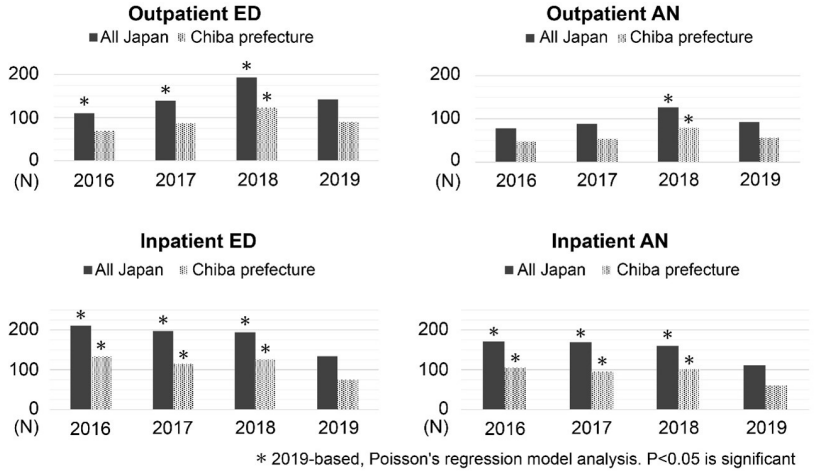

Figure 3. Changes in the number of outpatient and inpatient consultations at Kohnodai Hospital. Black bars indicate the patient number in all Japan groups. The striped bars indicate the patient number of Chiba prefecture group. Values for each year were compared using the 2019 data as the baseline. A *p*-value < 0.05 was considered significant.

Increase in BMI during hospitalization among patients with AN (Table 4, Figure 4)

Poisson's regression model did not demonstrate any significant difference in the number of inpatients with AN in the all-Japan and Chiba Prefecture groups during the 4-year time period. The BMI of the all Japan group increased significantly less during admission in 2016 (p = 0.009) and 2017 (p = 0.05) compared with that in 2019. There was no significant difference in the BMI during admission of the all-Japan group between 2018 and 2019. Similarly, the BMI of the Chiba Prefecture group increased significantly less during admission in 2016 (p = 0.011) and 2018 (p = 0.022) compared with that in 2019. Although some factors demonstrated differences at the national and prefectural levels, the mean values showed similar patterns.

Discussion

The number of consultations provided by our support center has increased yearly. The referral rate to other hospitals has also increased because we promote medical cooperation. During the same time period, we also noted a decrease in the number of outpatients and inpatients

Table 3. Basic data of ED and AN inpatients treated at Kohnodai Hospital over two weeks

	2016	2017	2018	2019	*p*
Inpatient ED					
Number of patients					
All Japan group	211	197	194	134*	*vs.* 2016, 2017, 2018
Chiba Prefecture group	133	115	126	74*	*vs.* 2016, 2017, 2018
Age at first visit (years)					
All Japan group	31.6 ± 0.8	33.1 ± 0.9	30.6 ± 0.9	33.1 ± 1.1	n.p.
Chiba Prefecture group	30.8 ± 1.0	30.7 ± 1.1	29.7 ± 1.1	31.3 ± 1.4	n.p.
Duration of illness (days)					
All Japan group	3,902.1 ± 232.1	4,073.5 ± 261.9	3,780.1 ± 232.8	4,585.3 ± 327.2	n.p.
Chiba Prefecture group	4,073.6 ± 292	3,490.1 ± 255.9	3,470.9 ± 243.2	4,390 ± 373.1	n.p.
Duration of hospitalization					
All Japan group	25.7 ± 2.4	28.4 ± 2.6	26.1 ± 2.3	31.8 ± 2.9	n.p.
Chiba Prefecture group	23.6 ± 2.2	23.6 ± 2.8	22.5 ± 2.3	35.6 ± 4.4	n.p.
Inpatient AN					
Number of patients					
All Japan group	171	169	160	111*	*vs.* 2016, 2017, 2018
Chiba Prefecture group	105	96	102	60*	*vs.* 2016, 2017, 2018
Age at first visit (years)					
All Japan group	32.9 ± 0.9	33.2 ± 1.0	31.2 ± 1.0	32.6 ± 1.2	n.p.
Chiba Prefecture group	32.2 ± 1.2	30.8 ± 1.2	29.9 ± 1.2	30.7 ± 1.5	n.p.
Duration of illness (days)					
All Japan group	4,287.9 ± 257.7	3,996 ± 277.4	3,962.9 ± 255.7	4,664.0 ± 357.2	n.p.
Chiba Prefecture group	4,594.4 ± 335.1	3,561.0 ± 285.2	3,664.6 ± 276.1	4,625.5 ± 424.1	n.p.
BMI at admission (kg/m^2)					
All Japan group	12.9 ± 0.2	13.1 ± 0.2	13.3 ± 0.2	12.9 ± 0.3	n.p.
Chiba Prefecture group	13.1 ± 0.3	13.1 ± 0.3	13.8 ± 0.3	12.7 ± 0.3*	*vs.* 2018, 2019
BMI at discharge (kg/m^2)					
All Japan group	13.2 ± 0.2	13.4 ± 0.2	13.7 ± 0.2	13.6 ± 0.3	n.p.
Chiba Prefecture group	13.4 ± 0.3	13.4 ± 0.3	14.1 ± 0.3	13.5 ± 0.3	n.p.
Duration of hospitalization (days)					
All Japan group	25.5 ± 2.8	29.4 ± 2.9	28.8 ± 2.8	32.5 ± 3.2	n.p.
Chiba Prefecture group	22.8 ± 2.4	24.5 ± 3.3	24.9 ± 2.7	36.9 ± 4.7*	*vs.* 2016, 2017, 2018

*p-value < 0.05.

Table 4. Increase in BMI among patients with AN during hospitalization at Kohnodai Hospital

Variables	2016	2017	2018	2019	*p*
Number of patients					
All Japan group	80	83	92	67	n.p.
Chiba Prefecture group	57	47	53	40	n.p.
Increase in BMI (kg/m^2)					
All Japan group	0.49 ± 0.13	0.60 ± 0.12	0.68 ± 0.15	1.08 ± 0.15*	*vs.* 2016, 2017
Chiba Prefecture group	0.38 ± 0.2	0.55 ± 0.2	0.44 ± 0.2	1.14 ± 0.2*	*vs.* 2016, 2018

*p-value < 0.05.

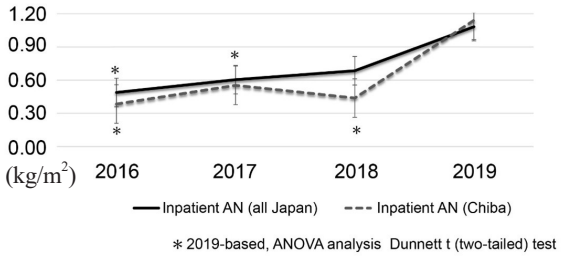

Figure 4. Increase in body mass index (BMI) over two weeks hospitalization at Kohnodai Hospital. This table summarizes the factors that showed significant differences over time. The horizontal axis indicates the fiscal year. Values for each year were compared using the 2019 data as the baseline. A *p*-value < 0.05 was considered significant.

treated for EDs in our hospital. Notably, patients with AN who were treated in our department demonstrated significant weight gain during hospitalization, which suggested that we were able to provide more effective treatment than previously possible.

This study analyzed the data of patients living in all regions of Japan and Chiba Prefecture separately. According to a survey conducted in 2016, Chiba Prefecture is a well-balanced metropolitan/rural area with a population of 6.23 million. It is the 6th most densely populated region in Japan. Chiba Prefecture boasts the 22nd highest per capita income, 10th highest total number of farms, and 9th highest number of

hospitals. The specialized treatment centers in Miyagi, Chiba, Shizuoka, and Fukuoka Prefectures had 169, 551, 208, and 227 consultations, ED outpatient visits, and inpatient admissions, respectively, between April 2018 and December 2018 (*11*). We considered Chiba Prefecture to be a useful metropolitan/rural model to evaluate the activities of the CSC in Japan.

Our results can be divided into three main categories: ED at the CSC, outpatient trends, and inpatient trends.

ED at the CSC

Before the CSC was established, there was a concern that ED centers would be regarded as special treatment facilities, which would result in an influx of patients with EDs and discourage other facilities from providing similar treatment. Our data suggested that while the number of consultations at the CSC increased annually, the total number of outpatients between 2018 to 2019 at Kohnodai Hospital decreased. These results clearly show that encouraging cooperation among the medical institutions in the prefecture led to good results. We did not examine the effectiveness of the various methods of medical cooperation we promoted in our prefecture, but we can presume that the visits to the medical institutions to promote medical cooperation and workshops on ED treatment were effective. Our publicity activities on social networking sites may have contributed to the success of the CSC. In the past, patients needed a referral from a clinician or an internet search to consult with our specialists or be treated at Kohnodai Hospital. Under the new program, patients were able to find us directly and get consultations easily, which could have been factors in the changes observed in this study. Further study will be necessary to confirm the relation of the above-mentioned factors to our results.

Outpatient trends in EDs and AN

While some years showed no significant statistical difference, the all Japan and Chiba Prefecture groups demonstrated similar outpatient trends. In the all Japan group, the number of outpatient consultations peaked in 2018 and decreased thereafter. In relation, the number of patients who presented at our department in 2019 decreased by 30%, which may be a result of the guidance service provided by the CSC. Among the EDs, AN presented as the most severe physically. It was also associated with the highest mortality rate (*2*). The age of the patients with AN in the all Japan group was significantly younger in 2019. The Chiba Prefecture group showed a similar trend, but it did not reach statistical significance. The activities of the support center may have contributed to the early detection and treatment of patients in the area. In long-term studies (> 20 years follow-up) that examined the prognosis of patients with AN or BN, one-third of the patients were not cured, and the median duration of the disease in patients with AN was 10 years (*1,2,12*). These data were based on patients who received previous treatment. One report noted that EDs lasted 10 years on average among patients who did not receive psychiatric treatment (*12*). It is possible that proactive treatment with early intervention can improve this prognosis (*1,2,12*).

Inpatient trends in EDs and AN

The support center significantly reduced the number of hospitalized patients in 2019. In the Chiba Prefecture group, the BMI values from 2019 decreased significantly compared with that in the previous year, whereas the BMI values during hospitalization increased significantly compared with those in 2016 and 2018. Moreover, the duration of hospitalization increased significantly compared with the previous three years. It is assumed that the increased length of stay is due to the fact that it is now possible to treat patients with more robust weight gain. We assumed that patients living in Chiba Prefecture were more affected by our support center activities than those living in other prefectures because of the medical cooperation within Chiba Prefecture. However, we did not observe a younger age of admission or shorter duration of illness, which are indicators of early detection of EDs. It will take several years before fruitful results can be seen. In addition, it will be possible to divide the roles of specialist hospitals for the treatment of severe AN with other hospitals. This will be possible in the future. It may take some time before the results start appearing.

The all-Japan group demonstrated a similar trend. Instead of decreasing the number of inpatients, we found that our facility was able to accept more patients with severe AN and provide aggressive inpatient treatment.

To prevent relapse, inpatient treatment of severe AN requires nutritional status improvement, psychotherapy and counseling for the patient's caregivers (*1,2*). In terms of integrated treatment, facilities specializing in EDs need to offer an environment that can focus on treating severely ill patients. A program that promotes medical cooperation is one such environment. The risk factors for severe and enduring AN include the length of illness and previous treatment failures (*13*). About 10% of ANs and 20% of BNs will have a prolonged eating disorder (*14*). They may be conceptualized as Severe and Enduring Eating Disorders (SEED) (*14*). They are characterized by a long duration of illness and multiple unsuccessful treatment attempts. As such, it is important to detect and treat AN early, as well as promptly initiate specialized treatments for patients who do not improve with normal measures.

This study's limitations include the short follow-up period of four years. For the data and our interpretations

to be more meaningful, there needs to be a division of roles between specialist hospitals and general hospitals, which will take several years to implement. Additionally, the situation of patients after referral needs to be investigated further. Increasing the number of referrals is an important issue to improve medical cooperation.

We assumed that the changes seen in our outpatients and inpatients could be attributed to the activities of the support center; however, a long-term study may be necessary.

In conclusion, promoting medical cooperation among specialized hospitals allowed these institutions to provide better and more intensive care for patients with severe EDs.

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Evaluating the daily life of child and adolescent psychiatric outpatients during temporary school closure over COVID-19 pandemic: A single-center case-control study in Japan

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Abstract: This study evaluated the clinical characteristics of mental health of child and adolescent psychiatric patients during temporary school closure throughout the coronavirus 2019 (COVID-19) pandemic in Japan using the Questionnaire - Children with Difficulties (QCD) and other useful psychological rating scales. The participants were those who visited the Department of Child and Adolescent Psychiatry, Kohnodai Hospital. From those 1,463 participants, case and control groups were selected: 92 patients who visited the hospital during the temporary school closure from March 2020 to May 2020 (case group) and randomly sampled sex- and age-matched 92 patients during the pre-COVID period from April 2017 to March 2020 (control group). QCD is a parent-assessed questionnaire designed to evaluate the difficulties of children along the course of a day, right from waking up in the morning to retiring to bed at night. Lower scores indicate stronger difficulties. QCD scores were compared between the two groups in each of the following age groups: elementary school (6-12 years of age) and junior high school (12-15 years of age). In elementary school students, scores "during school" of QCD indicating functioning or disabilities during school hours were 3.31 ± 2.52 and 4.52 ± 2.33 in case group and control group, respectively ($p < 0.05$). In junior high school students, scores "Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS)" indicating ADHD symptoms were 16.78 ± 12.69 and 11.80 ± 10.40 in case group and control group, respectively ($p < 0.05$). The findings suggest that the closure of schools due to the pandemic might worsen difficulties among elementary school patients, and hyperactivity and impulsivity might increase among junior high school patients. The long-term impact of stress caused by school closure on child and adolescent psychiatric patients needs to be investigated in the future.

***Keywords*:** Questionnaire - Children with Difficulties (QCD), clinical characteristics, during school, Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS), hyperactivity and impulsivity

Introduction

Coronavirus disease 2019 (COVID-19), which emerged in December 2019, turned into a pandemic and spread worldwide in 2020 (*1*). The social distancing measures adopted for preventing the spread of the infection disrupted the daily routine of people. According to United Nations Educational, Scientific and Cultural Organization (UNESCO), as of April 1, 2020, schools were suspended nationwide in 172 countries (*2*). In Japan, owing to the spread of COVID-19, school closures continued from March 2, 2020, to May 25, 2020. The children were forced to stay at home to curb the infection and were hence unable to lead normal lives. School is crucial to help maintain mental health function as a mental health system for children and adolescents with and without mental health issues (*3-5*).

COVID-19 is associated with psychiatric problems in several groups, including patients affected by the disease and clinicians who care for them (*6,7*). Furthermore, COVID-19 is linked to psychiatric symptoms in the general population of adults and children as well (*8*). Children who were quarantined at home experienced symptoms of anxiety, depression, and post-traumatic

stress disorder (*9,10*). People with mental health disorders are especially vulnerable during times of crisis (*11*). The effects of COVID-19 on the mental state of general children have been examined, but how are children with mental problems affected?

There are some studies on the effects of temporary school closure on the mental health of children. An increased risk of emotional and behavioral problems was reported among adolescents in Indonesia (*12*). Children who were physically active during school closures had fewer behavioral problems. Children of parents with anxiety symptoms were at higher risk for emotional symptoms (*13*). Loneliness during school closures was associated with gaming addiction behaviors among young people (*14*). School closures due to the COVID-19 outbreak caused anxiety, depression, and stress in children (*15*). Children with poor academic performance were associated with higher risk of anxiety-related and obsessive compulsive disorder-related symptoms (*16*). In a study of Japanese elementary and junior high school students, the school closures disrupted their sleep rhythms, eating habits, and physical activity. As a result, children became less active and energetic, and found it harder to find things that interested them (*17*). The effects of temporary school closure on the mental state of general children have been examined, but how did the lives of children with mental problems change between temporary school closure compared to the pre-COVID period? In the normal period, the prevalence of bullying among children with Autism Spectrum Disorders (ASD) or attention-deficit hyperactivity disorder (ADHD) was high (*18*). Bullying was related to having ADHD, lower social skills, and some form of conversational disability (*19*).

This study aimed to evaluate the clinical characteristics of the child and adolescent psychiatric patients in the period of temporary school closure during COVID-19. Temporary school closure during COVID-19 is expected to have some effect on difficulties in their daily life.

Participants and Methods

Study design and setting

The present study used data from Registry Study of Child and Adolescent Mental Health in Japan (*http://www.ncgmkohnodai.go.jp/subject/100/200/opt10018111401.pdf*). The participants comprised patients who visited Department of Child and Adolescent Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, between April 2017 and May 2020 for the first time. A retrospective case-control design was utilized to evaluate patients' daily lives throughout temporary school closure during the COVID-19 pandemic. First, the participants were allocated to one of the following two groups: patients who visited the hospital during the temporary school closure from March 2020 to May 2020 and patients who visited the hospital from April 2017 to March 2020. Second, patients with incomplete data and preschool patients were excluded from the former group. They were case group. The same number of sex- and age-matched patients with case group was randomly sampled from the latter group. They were control group. The two groups were compared in each age category: elementary school patients (6-12 years of age) and junior high school patients (12-15 years of age). The Questionnaire - Children with Difficulties (QCD) is a parent-assessed questionnaire designed to evaluate difficulties in a child's functioning during specific periods of the day (*20*). The QCD scores were compared between case and control groups. Furthermore, five other psychological rating scales were used for the comparison, namely, Tokyo Autistic Behavior Scale (TABS) (*21*), Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) (*22*), Oppositional Defiant Behavior Inventory (ODBI) (*23*), Depression Self-Rating Scale for Children (DSRS) (*24*), and Spence Children's Anxiety Scale (SCAS) (*25*).

The study protocol was approved by Ethical Committee of National Center for Global Health and Medicine (NCGM-G-003603-00) (Tokyo, Japan) and was conducted in accordance with the tenets of Declaration of Helsinki. There was no written or verbal informed consent because informed consent was obtained from all participants as per Ethical Guidelines for Medical and Health Research Involving Human Subjects of Japan. The guidelines state that, "it is not always necessary to obtain informed consent from study participants. However, researchers must publish information on the implementation of the study, including the purpose of the study for observational studies only using past clinical records and not human tissue samples". The purpose, methods, and analyses of the study and the details on how to refuse participation were posted in the hospital outpatient clinic. In addition, the data were anonymized throughout the study period. Information from this study may contain potentially identifiable patient information, and data sharing is restricted by Ethical Committee of National Center for Global Health and Medicine based on Ethical Guidelines for Medical and Health Research Involving Human Subjects of Japan. However, the data can be accessed by contacting Ethical Committee of National Center for Global Health and Medicine.

Recruitment of participants

This study comprised Japanese patients who visited our department between April 2017 and May 2020. We allowed consultation of patients < 15 years of age at the initial visit. Psychologists and psychiatrists designed the initial interview forms, which included the demographic characteristics of the patients and clinical

implications. Subsequently, the questionnaires were constructed using QCD, TABS, ADHD-RS, ODBI, DSRS, and SCAS. Professionals specializing in child and adolescent psychiatry diagnosed and treated all patients according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (*26*). Patients with a moderate-to-severe intellectual disability according to DSM-5, organic brain disease, drug-induced psychiatric disease, traumatic brain injury, and genetic syndromes were referred to other medical institutions and were excluded from this study.

Measurement tools

QCD: This questionnaire consists of a total of 20 questions designed to assess the child's daily life functioning or disabilities along the course of a day, right from waking up in the morning to retiring to bed at night (Supplemental Appendix 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=48*). This form is filled out by caregivers. Each item is provided with a score of 0-3, and a score of 0 indicates the most severe condition (*20*). The reliability and validity of this questionnaire have been established (*27*).

TABS: This tool is rated by the child's caretaker to assess the behavior of children with ASD. The tool comprises 39 items that are provisionally grouped into the following four areas: interpersonal-social relationship, language-communication, habit-mannerism, and others. Each item has a score of 0-2, and the highest possible total score is 78. The higher the score, the stronger are the autistic characteristics (*21*).

ADHD-RS: This is an 18-item tool used by the child's caretaker to assess ADHD symptoms (*22*). Takayanagi *et al.* standardized Japanese version of ADHD-RS, which includes two factors: hyperactivity/impulsiveness and inattention. Each item is provided with a score of 0-3, and a total score of 54 indicates a condition of the highest severity (*28*).

ODBI: This comprises 18 questions covering DSM-IV-TR diagnostic criteria for ADHD, Oppositional Defiant Disorder (ODD), and conduct disorder. Each item is provided with a score of 0-3, and a total score of 54 indicates the highest severity. Participants with ODBI scores > 20 are considered to have ODD (*23*).

DSRS: This is a self-rating scale for depression in childhood. The 18-item scale was established based on a 37-item inventory associated with major depressive syndromes. Each item is provided with a score of 0-2, and a total score of 36 suggests the highest severity (*24*). Denda investigated Japanese children and adolescents, and the results showed that a cutoff score of 15 can be used to demonstrate the risk of depression (*29*).

SCAS: This questionnaire can evaluate the symptoms of various anxiety disorders, particularly social phobia, obsessive-compulsive disorder, and panic disorder/agoraphobia. The 38-question test can be filled out by the child or the parent. Each item is provided with a score of 0-3, and a score of 114 is suggestive of the most severe condition (*25*). The internal consistency and test-retest reliability was satisfied in Japanese children and adolescents (*30*).

Statistical analysis

Mann-Whitney *U* test was employed to compare the continuous variables between the two groups. All statistical tests were two-tailed, and p-values < 0.05 were considered statistically significant. The analyses were performed using the Easy R Package, version 1.40 (*31*).

Results

Participants and Descriptive Data

Figure 1 depicts the flowchart of the participants. From April 2017 to May 2020, 1463 patients consulted our

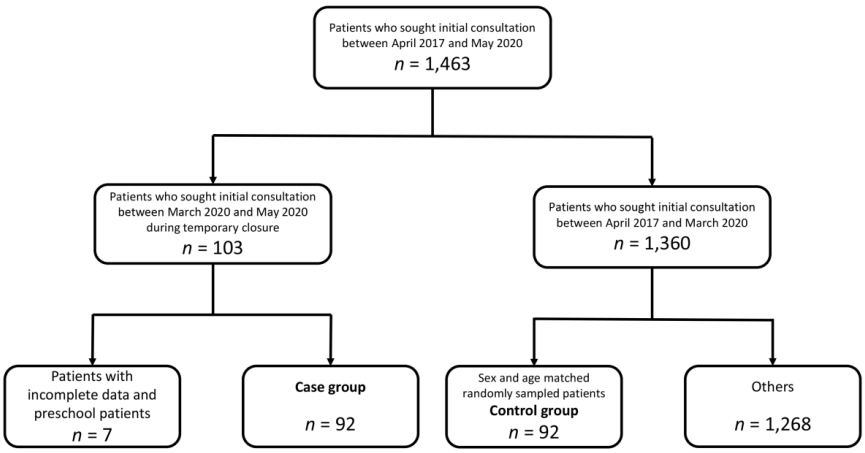

Figure 1 .The flowchart of the participants.

department. From March 2020 to May 2020, which corresponds to the temporary school closure period, 103 patients came for consultation; from April 2017 to March 2020, 1360 patients came for consultation. When we excluded those with incomplete data and preschool patients, case group consisted of 92 patients, and control group consisted of 92 randomly sampled sex- and age-matched patients.

Of the 92 patients, 42 were elementary school students (27 males, 15 females) and 50 were junior high school students (21 males, 29 females). The average age of the elementary school students was 9.29 ± 1.70 years (range, 6-12 years). The average age of the junior high school students was 13.32 ± 0.71 years (range, 12-15 years). Tables 1 and 2 present the clinical characteristics of elementary and junior high school students, respectively (both case and control groups). Each parameter was a result of Mann-Whitney *U* test.

In elementary school students, total scores of QCD were 24.26 ± 11.83 and 28.69 ± 8.69 in case group and control group, respectively. In junior high school students, total scores of QCD were 26.82 ± 12.11 and 24.96 ± 12.29 in case group and control group, respectively. Tables 3 and 4 present the QCD scores of elementary and junior high school students, respectively. Each parameter was the result of Mann-Whitney *U* test.

Outcome Data

In elementary school students, there were no significant differences in TABS, ADHD-RS, ODBI, DSRS, and SCAS scores between the two groups (Table 1).

In junior high school students, there were no significant differences in TABS, ODBI, DSRS, and SCAS scores between the two groups. Scores "ADHD-RS" indicating ADHD symptoms were 16.78 ± 12.69 and 11.80 ± 10.40 in case group and control group, respectively ($p < 0.05$) (Table 2).

In elementary school students, scores "during school" of QCD indicating functioning or disabilities during school hours were 3.31 ± 2.52 and 4.52 ± 2.33 in case group and control group, respectively ($p < 0.05$) (Table 3).

In junior high school students, there were no significant differences in the QCD scores between the two groups in either the main category or the subcategories (Table 4).

Discussion

This is the first study to evaluate the daily life functioning or disabilities of child and adolescent psychiatric patients along the course of a day in the period of temporary school closure during COVID-19. No articles were found in the PubMed title search that contain all the words "closure", "patient", and "COVID".

In elementary school students, the subcategory score "during school" of QCD was significantly lower in case group than in control group. "During school" included the following questions: "Does your child like going to school"? "Can your child behave in class as other children

Table 1. Clinical characteristics of elementary school students

Variables	Case, % (*n* = 42)	Control, % (*n* = 42)	Effect Size	*p* value
Age (mean ± standard deviation)	9.29 ± 1.70	9.29 ± 1.70	-	-
Male sex (%)	64.3 (*n* = 27)	64.3 (*n* = 27)	-	-
TABS score	17.86 ± 10.80	16.45 ± 9.69	0.14	NS
ADHD-RS	20.64 ± 13.79	19.98 ± 11.02	0.05	NS
ODBI	24.12 ± 17.24	26.40 ± 14.86	0.14	NS
DSRS	11.93 ± 5.27	13.71 ± 6.09	0.31	NS
SCAS	29.02 ± 19.22	33.88 ± 18.85	0.26	NS

Score ranges: Age, 6-12 years old. TABS (Tokyo Autistic Behavior Scale): 0-78 points. ADHD-RS (ADHD-Rating Scale): 0-54 points. ODBI (Oppositional Defiant Behavior Inventory): 0-54 points. DSRS (Depression Self-Rating Scale for Children): 0-36 points. SCAS (Spence Children's Anxiety Scale): 0-114 points.

Table 2. Clinical characteristics of junior high school students

Variables	Case, % (*n* = 50)	Control, % (*n* = 50)	Effect Size	*p* value
Age (mean ± standard deviation)	13.32 ± 0.71	13.32 ± 0.71	-	-
Male sex (%)	42.0 (*n* = 21)	42.0 (*n* = 21)	-	-
TABS score	13.0 ± 11.49	10.5 ± 9.26	0.24	NS
ADHD-RS	16.78 ± 12.69	11.80 ± 10.40	0.43	$p < 0.05$
ODBI	17.68 ± 13.52	19.00 ± 14.06	0.10	NS
DSRS	15.74 ± 8.37	16.52 ± 8.00	0.10	NS
SCAS	35.38 ± 23.39	34.02 ± 21.00	0.06	NS

Score ranges: Age, 12-15 years old. TABS (Tokyo Autistic Behavior Scale): 0-78 points. ADHD-RS (ADHD-Rating Scale): 0-54 points. ODBI (Oppositional Defiant Behavior Inventory): 0-54 points. DSRS (Depression Self-Rating Scale for Children): 0-36 points. SCAS (Spence Children's Anxiety Scale): 0-114 points.

Table 3. The QCD scores of elementary school students

QCD	Case, % (n = 42)	Control, % (n = 42)	Effect Size	p value
Total	24.26 ± 11.83	28.69 ± 8.69	0.43	NS
Morning	6.00 ± 3.12	6.62 ± 3.12	0.20	NS
During school	3.31 ± 2.52	4.52 ± 2.33	0.50	$p < 0.05$
After school	3.55 ± 2.41	4.57 ± 2.50	0.42	NS
Evening	5.50 ± 3.48	6.00 ± 2.59	0.16	NS
Night	2.62 ± 2.67	2.83 ± 2.33	0.08	NS
Overall behavior	3.29 ± 1.99	4.14 ± 1.42	0.49	NS

Score ranges: QCD (Questionnaire: Children with Difficulties): 0-60 points.

Table 4. The QCD scores of junior high school students

QCD	Case, % (n = 50)	Control, % (n = 50)	Effect Size	p value
Total	26.82 ± 12.11	24.96 ± 12.29	0.15	NS
Morning	6.06 ± 3.37	5.40 ± 3.52	0.19	NS
During school	3.92 ± 2.63	4.00 ± 2.56	0.03	NS
After school	4.08 ± 2.58	3.88 ± 2.54	0.08	NS
Evening	5.14 ± 3.01	4.48 ± 3.32	0.21	NS
Night	4.28 ± 2.62	3.74 ± 2.61	0.21	NS
Overall behavior	3.44 ± 1.84	3.46 ± 1.98	0.01	NS

Score ranges: QCD (Questionnaire: Children with Difficulties): 0-60 points.

do"? and "Does your child have friends who accept him/her at school"? A score of 0 means "completely disagree", and a score of 3 means "completely agree". Parents might have given low scores because schools did not function during the temporary closure. The closure of schools due to the pandemic might worsen difficulties among elementary school patients. 41.0% of elementary school students and 84.3% of junior high school students used the Internet on their own smartphones, with the usage rate increasing with age (*32*). Therefore, parents of children attending junior high school might have given the same score as in normal times because their children were connected with their friends online. Parents of school-refusing adolescents had lower levels of parental self-efficacy than parents of school-attending adolescents (*33*). As another reason why parents gave low evaluation, it could be a burden for parents have their children stay at home even if it is for the temporary closure. Patients were affected by temporary school closure and out of shape during "during school".

In junior high school students, there were no significant differences in the QCD scores between the two groups. The total score of ADHD-RS was significantly higher in case group than in control group. As a previous study had suggested that ADHD symptoms were positively associated with perceived stress (*34*), patients in the age group of junior high school might have been frustrated by the temporary school closure as it prevented them from socializing with their peers. No diagnosis has been made as this is the initial consultation, but it might be that many children are diagnosed with ADHD. This result might suggest that hyperactivity and impulsivity are increasing but not affecting daily life functioning. In a previous study using QCD, 298 children with ADHD faced greater difficulties, particularly in the evening compared with the community controls (*35*). Furthermore, these difficulties were related to the severity of ADHD symptoms (*35*). Due to the small sample size, no statistically significant differences were found, but parents may have difficulties in the evening.

The present study has some limitations to consider. First, measurement bias might have existed. Data were registered after the initial consultation. Additional information might have been obtained after further examinations. Second, a selection bias may exist because of several reasons. There were only 92 participants who belonged to case group. Due to the small sample size, the results might be subject to random errors. Further, the small sample size might have contributed to no significant differences in the proportion. The study did not represent the overall situation associated with child and adolescent psychiatric patients throughout the temporary school closure during COVID-19 because it was conducted in a single district. Finally, the results of this study confirmed the association between the child and adolescent psychiatric patients and the daily life functioning or disabilities throughout the temporary school closure during COVID-19, but not the causality. An investigation of the effects of each of the two factors, *i.e.*, temporary school closure and COVID-19 pandemic, on daily life functioning or disabilities is a future challenge.

Conclusion

This study evaluated the clinical characteristics of the

child and adolescent psychiatric patients throughout the temporary school closure during COVID-19. In line with the retrospective case-control design, the participants were allocated to one of the following two groups: those who visited the hospital during temporary school closure (case group) and randomly sampled sex- and age-matched patients (control group). Psychiatric outpatients of elementary school showed difficulties during school time due to temporary school closure throughout the COVID-19 pandemic. In psychiatric outpatients of junior high school, the total score of ADHD-RS was significantly higher in the case group than in the control group. Further investigations are warranted to study the impact of long-term stress experienced by child and adolescent psychiatric patients due to the school closure.

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Changes in parental involvement and perceptions in parents of young children during the COVID-19 pandemic: A cross-sectional observational study in Japan

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Abstract: This study aimed to clarify changes in parental involvement with their children and parental perceptions related to parenting in both fathers and mothers of young children during the coronavirus disease 2019 (COVID-19) pandemic. A cross-sectional observational design was used. Data were collected using a web-based questionnaire from 28 fathers and 115 mothers between October 1 and November 30, 2020. Parents answered questions regarding themselves, basic sociodemographic variables, perceived changes in involvement with their children, the presence or absence of abusive behavior (*e.g.*, violence toward children), and parental perceptions related to parenting. Many parents indicated that they did not experience major changes in their involvement or perceptions compared to before the COVID-19 pandemic. Half of the fathers considered themselves to be in more physical contact or communication with their children; there was a significant difference between fathers and mothers regarding eating meals with their children ($p = 0.00$). Fathers felt tired due to parenting (35.7%) or a lack of free time (42.9%) during the COVID-19 pandemic. While significantly more mothers than fathers responded that their partners took care of their children ($p = 0.03$), significantly greater number of mothers than fathers also reported feeling overburdened ($p = 0.00$). Family support workers should help fathers maintain involvement with their young children without high stress levels and support mothers to reduce their heavy burden of parenting continuously. This would contribute to young children's growth and development despite a public health crisis.

***Keywords*:** parenting, mothers, fathers, infants, preschool children

Introduction

The coronavirus disease 2019 (COVID-19) has wrought havoc worldwide. Every government implemented measures to prevent COVID-19's spread. In Japan, the government announced the first state of emergency on April 7, 2020, and later issued it several times in areas with many patients with COVID-19. The Japanese government did not carry out a lockdown like other countries but tackled COVID-19's spread through defensive measures such as recommendations to avoid the "Three Cs" which are closed spaces, crowded places, and close-contact settings. The government also recommended staying at home to limit the flow of people and reduce the spread of the virus. Although these measures did not have legal force, social systems have changed in various ways in response to the recommendations, requiring people to drastically change their lifestyle and adapt. Some people were able to adapt to changes well, while others were not. If we consider the change in parents' lifestyles and interactions with children, adaptive parents increased their time at home smoothly and shared parenting and household chores among each other (*1,2*). However, some parents' household-related burdens or parenting stress increased by staying at home (*3,4*).

Previous studies on parents' lifestyles during the COVID-19 pandemic in other countries have reported similar trends. Many parents, mostly mothers, experienced difficult adjustments in dividing time between parenting and work, heavy responsibility for additional household chores and parenting, or isolation under lockdown (*5-9*). We should pay attention to the harmful effects on parents who could not adapt to changes after the COVID-19 pandemic. They also have some mental health problems, such as high levels of anxiety, depressive symptoms, and parenting stress (*7,10-13*). Sometimes, parenting burden or parental mental health problems have a negative effect on parents' involvement with their children and perceptions related to parenting. In fact, previous studies have reported that tiredness caused by parenting

burden increases parental negative emotions toward parenting, and parents who have suffered health losses display a negative attitude toward their children (*14-17*). However, there is a lack of studies regarding changes in parental involvement and perceptions during the COVID-19 pandemic.

The COVID-19 pandemic has imposed many limits on young children and their parents. In Japan, many institutions restricted young children and their parents to utility time, or the number of users was restricted to avoid the Three Cs. The number of parents who did not admit their children in day nurseries or to undergo medical examinations also increased to prevent coronavirus infections (*18,19*). As a result, contact between parents and family support workers decreased. In other words, not only did parents lose opportunities to seek support regarding matters relating to parenting or their children, but it also became difficult for family support workers to understand the conditions of parents and their children after the pandemic. Timely support for parents became difficult when they faced parenting problems. It can be considered that a lack of parental support leads to inappropriate parenting. In fact, a previous study reported that some parents felt that their psychological or social resourses were fewer than before the COVID-19 pandemic (*20*). Young children tend to become targets of inappropriate parenting and are more susceptible to abuse than older children before the COVID-19 pandemic (*21-23*). However, there is also a lack of studies focusing on parents of young children after the COVID-19 pandemic.

We consider that it is necessary for family support workers to be mindful of the changes in parenting due to the COVID-19 pandemic and to provide additional support to parents. This study aimed to clarify changes in parental involvement with their children and perceptions related to parenting by fathers and mothers of young children during the COVID-19 pandemic. Based on the results of this study, we suggest ways in which support can be provided to fathers and mothers.

Materials and Methods

Participants

In this study, young children were defined as those aged six years old or less. We included parents whose children used institutions to cooperate in this study. Parents who could not read and answer the questionnaire written in Japanese or did not agree to participate in this study were excluded. The final participants of this study were 143 parents (28 fathers and 115 mothers).

Measures

Demographic data

Parents answered questions regarding their age, family structure, years of education, employment status, annual household income, children's age, children's sex, and the number of children in the family.

Parental perceptions related to parenting

We explored parental perceptions related to parenting during the COVID-19 pandemic using a questionnaire (Supplemental Table 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=47*) created for this study based on previous studies (*18,24,25*). The topics were perceived changes in interactions, the presence or absence of abusive behaviors toward young children, and perceptions related to parenting compared to before the COVID-19 pandemic. Parental abusive behavior is defined as any parental behavior that harms children, such as being physically violent toward a child or rejecting a child. Regarding perceived changes in the frequency of interactions compared to before the COVID-19 pandemic, parents were asked the following about their interactions with their children: daily care, playing, physical contact, communication, and eating a meal, using a five-point Likert-type scale ranging from *decreased very much* (0) to *increased very much* (4).

Parental abusive behavior was assessed using five items of parental performance: punching or kicking, shouting emotionally, cursing or threatening, parental neglect, and ignoring children. Participants chose the most closely applied answer regarding abusive behavior from four possible choices (*doing before but not after the pandemic, not doing before but doing after the pandemic, not doing both before and after the pandemic,* or *doing both before and after the pandemic*).

Regarding perceptions related to parenting, respondents answered the following seven questions: (a) I feel that my family bonds are strong, (b) I enjoy interaction with my children, (c) I feel pleasure in my children's growth, (d) I feel my partner takes care of the children, (e) I feel tired due to parenting, (f) I do not have enough free time, and (g) I cannot interact with the children because I am overburdened. Parents responded on a five-point Likert-type scale ranging from *strongly disagree* (0) to *strongly agree* (4).

Data collections

We conducted a web-based questionnaire survey in Tokyo. We sent letters with written requests for cooperation in this study to 23 nursery schools, six kindergartens, and three childcare support centers in one city in Tokyo. We explained the contents of this study to the managers or staff of these institutions who agreed to cooperate with this study before data collection. We requested that the institutions inform only parents who had children aged six years or younger. Information for inviting parents to participate in this study was provided by the managers or staff. Participants were recruited

between October 1st and November 30th, 2020, when the second wave of COVID-19 subsided in Japan. The online questionnaire was shared with participants during the same period. The opening page of the online questionnaire explained the study, including the purpose, methods, voluntary participation, anonymity, and contact information.

Statistical analysis

Categorical variables were presented as numbers and percentages, and continuous variables as mean and standard deviation (*SD*). We conducted the following analyses to explore statistical differences between fathers and mothers: (a) categorical variables were tested using the chi-square test or Fisher's exact test, and (b) parental years of education were examined using the Mann-Whitney U test. We conducted a residual analysis to explore which cells contributed to the significant association if we found significant differences using the chi-square test or Fisher's exact test in the three groups. Usually, adjusted residuals of ±1.96< and ±2.58< indicate $p < 0.05$ and $p < 0.01$, respectively. We used the Shapiro-Wilk test to assess the normality of distribution of the continuous variables.

We focused on parents who changed their abusive behavior before and after the COVID-19 pandemic. We conducted the McNemar test to explore the statistical differences in the presence or absence of abusive behavior before and after the pandemic.

We summarized several responses to control variables as follows: (a) the responses for perceived changes of interaction frequency were "*increase*", "*static*", or "*decrease*", and (b) the responses for perceived changes of parental perceptions were "*agree*", "*static*", or "*disagree*".

To calculate the appropriate sample size for comparison between two groups, we set up as follows: (a) effect size was 0.5, (b) level of significance was 0.05, (c) statistical power was 0.8. We estimated the rate of data unavailability at 20%. Eventually, we would need to enroll 80 parents for each groups. We conducted data analysis after excluding data items with missing values. Two-tailed P-values less than 0.05 were considered significant. The analysis was conducted using the IBM SPSS Statistics ver. 25 and R version 3.6.3.

Ethics

The study protocol was approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval no: NCGM-G-003636-00). Before data collection, an anonymous survey was conducted. We confirmed the consent of the participants in this study using a checkmark placed by the participant in the confirmation box, which indicated the consent of the participant.

Results and Discussion

Table 1 shows the demographic data of the participants. The average number of education years was 15.9 (*SD*: 1.9) in fathers and 14.8 (*SD*: 1.6) in mothers. The average age of the children in fathers' group was 3.0 (*SD*: 1.7) and in mothers' group was 3.4 (*SD*: 1.8), and the ratio of boys to girls was one to one for both fathers and mothers. There was no significant difference between fathers and mothers in terms of demographic data, excluding years of education ($p = 0.04$) and employment status ($p = 0.00$). Most participants had a middle-to-high socioeconomic status.

In Table 2, we report the perceptions of changes in interaction frequency compared to before the COVID-19 pandemic. There was a significant difference between parents regarding eating with children ($p = 0.00$). Fathers eat meals with their children more often than before the COVID-19 pandemic.

Table 3 illustrates the perceived changes in the presence or absence of parental abusive behavior before and after the COVID-19 pandemic. There were no significant differences in abusive behavior between fathers and mothers.

Table 4 depicts the changes in parental perceptions related to parenting compared to before the first wave of the COVID-19 pandemic in Japan. There were significant differences between parents regarding partner's parenting ($p = 0.03$) and being overburdened ($p = 0.00$). Mothers indicated that fathers took part in parenting more than before COVID-19, and they were overburdened by parenting during the COVID-19 pandemic.

Most fathers answered that they did not feel any changes regarding their involvement with their young

Table 1. Participants' demographic data

Variables	Fathers *n* (%)	Mother *n* (%)	$p^{\dagger}$
Age (years)			0.81
20-29	1 (3.6)	6 (5.2)	
30-39	16 (57.1)	72 (62.6)	
> 40	11 (39.3)	37 (32.2)	
Employment Status			0.00**
Employed	26 (92.9)	68 (59.1)	
Not employed	2 (7.1)	47 (40.9)	
Family structure			1.00
Single-parent	0 (0.0)	4 (3.5)	
Two-parents	28 (100.0)	111 (96.5)	
Number of Children			0.12
1	13 (46.4)	34 (29.6)	
≥ 2	15 (53.6)	81 (70.4)	
Family Income (ten thousand yen)			0.10
< 300	1 (3.6)	6 (5.2)	
300-700	11 (39.3)	64 (55.7)	
> 700	14 (50.0)	32 (27.8)	
Non-response	2 (7.1)	13 (11.3)	

†Chi-square test or Fisher's exact test. ** $p < 0.01$.

Table 2. Comparison of perceptions of changes in interaction frequency in fathers and mothers

Perceptions	Fathers *n* (%)	Mother *n* (%)	$p^{\dagger}$
Daily care for children			0.58
increase	10 (35.7)	32 (27.8)	
static	18 (64.3)	79 (68.7)	
decrease	0 (0.0)	4 (3.5)	
Playing with children			0.60
increase	13 (46.4)	42 (36.5)	
static	14 (50.0)	66 (57.4)	
decrease	1 (3.6)	7 (6.1)	
Physical contact with children			0.09
increase	14 (50.0)	33 (28.7)	
static	13 (46.4)	77 (67.0)	
decrease	1 (3.6)	5 (4.3)	
Communication with children			0.07
increase	14 (50.0)	31 (27.0)	
static	14 (50.0)	79 (68.7)	
decrease	0 (0.0)	4 (3.5)	
Non-response	0 (0.0)	1 (0.8)	
Eating a meal with children			0.00**
increase	8 (28.6)	1 (0.8)	
Adjusted residual‡	5.41**	-5.41**	
static	19 (67.9)	112 (97.4)	
Adjusted residual‡	-5.06**	5.06**	
decrease	1 (3.6)	2 (1.7)	
Adjusted residual‡	0.61	-0.61	

†Chi-square test or Fisher's exact test. ** $p < 0.01$. ‡Adjusted residual: We conducted residual analysis to explore which cells contribute to the significant association if we found significant differences using the chi-square test or Fisher's exact test in the three groups. Usually, adjusted residual of ± 1.96 < and ± 2.58 < indicate $p < 0.05$ and $p < 0.01$.

children or their perceptions of parenting. Rather, the paternal frequency of interactions with their young children increased more than that of mothers. This finding is similar to that of previous studies (*9,26,27*). In particular, regarding eating meals with their children, there was a significant difference between fathers and mothers. This suggests that some fathers may have adapted well to the changes during the COVID-19 pandemic due to a shift in their lifestyle, such as eating at the same time as their young children. Moreover, 50% of the fathers agreed that their physical contact or communication with their children increased. We considered that changes in paternal lifestyle due to the COVID-19 pandemic increased positive father-child interactions. In addition, two-fifths of the fathers reported that they enjoyed interacting with their children (39.9%) and felt pleasure in their children's growth (46.4%). In other words, some fathers had positive parenting experiences during the COVID-19 pandemic. Parents' positive emotions toward their children can help relieve stress and moderate negative experiences for both parents and children (*28*). A previous study also reported that more fathers were involved with their children, and that more children's emotional well-being increased during the COVID-19 pandemic (*29*). Therefore, it is important for fathers to receive support to maintain their positive involvement with their children, as this benefits the children's healthy growth.

There is a risk that an exponential increase in the

Table 3. Comparison of perceptions of changes in the presence or absence of parental abusive behavior

Perceptions	Fathers *n* (%)	$p^{\dagger}$	Mother *n* (%)	$p^{\dagger}$
Punching or kicking		1.00		1.00
doing before but not after the pandemic	1 (3.6)		2 (1.7)	
not doing before but doing after the pandemic	1 (3.6)		3 (2.6)	
not doing both before and after the pandemic	23 (82.1)		99 (86.1)	
doing both before and after the pandemic	3 (10.7)		11 (9.6)	
Non-response	0 (0.0)		1 (0.8)	
Shouting emotionally		1.00		0.07
doing before but not after the pandemic	1 (3.6)		1 (0.8)	
not doing before but doing after the pandemic	1 (3.6)		7 (6.1)	
not doing both before and after the pandemic	21 (75.0)		55 (47.8)	
doing both before and after the pandemic	5 (17.9)		51 (44.3)	
Non-response	0 (0.0)		1 (0.8)	
Cursing or threatening		1.00		0.06
doing before but not after the pandemic	0 (0.0)		0 (0.0)	
not doing before but doing after the pandemic	1 (3.6)		5 (4.3)	
not doing both before and after the pandemic	24 (85.7)		101 (87.8)	
doing both before and after the pandemic	3 (10.7)		8 (7.0)	
Non-response	0 (0.0)		1 (0.8)	
Parental neglect		1.00		1.00
doing before but not after the pandemic	0 (0.0)		0 (0.0)	
not doing before but doing after the pandemic	1 (3.6)		0 (0.0)	
not doing both before and after the pandemic	27 (96.4)		115 (100.0)	
doing both before and after the pandemic	0 (0.0)		0 (0.0)	
Ignoring children		1.00		0.50
doing before but not after the pandemic	0 (0.0)		0 (0.0)	
not doing before but doing after the pandemic	1 (3.6)		2 (1.7)	
not doing both before and after the pandemic	25 (89.3)		106 (89.8)	
doing both before and after the pandemic	2 (7.1)		6 (5.2)	
Non-response	0 (0.0)		1 (0.8)	

†McNemar test.

Table 4. Comparison of changes in parental perceptions related to parenting in fathers and mothers

Perceptions	Fathers *n* (%)	Mother *n* (%)	$p^{\dagger}$
I feel that my family bonds are strong.			0.33
Agree	10 (35.7)	43 (37.3)	
Static	16 (57.1)	70 (60.9)	
Disagree	2 (7.1)	2 (1.7)	
I enjoy interaction with my children.			0.40
Agree	11 (39.3)	30 (26.1)	
Static	15 (53.6)	76 (66.1)	
Disagree	2 (7.1)	8 (7.0)	
Non-response	0 (0.0)	1 (0.8)	
I feel pleasure in my children's growth.			0.27
Agree	13 (46.4)	54 (47.0)	
Static	14 (50.0)	61 (53.0)	
Disagree	1 (3.6)	0 (0.0)	
I feel my partner takes care of the children.			0.03*
Agree	4 (14.3)	42 (36.5)	
Adjusted residual‡	-2.37*	2.37*	
Static	23 (82.1)	62 (53.9)	
Adjusted residual‡	2.55*	-2.55*	
Disagree	1 (3.6)	7 (6.1)	
Adjusted residual‡	-0.56	0.56	
Not having partner	0 (0.0)	4 (3.5)	
I feel tired due to parenting.			0.37
Agree	10 (35.7)	56 (48.7)	
Static	18 (64.3)	57 (49.6)	
Disagree	0 (0.0)	1 (0.8)	
Non-response	0 (0.0)	1 (0.8)	
I do not have enough free time.			0.37
Agree	12 (42.9)	57 (49.6)	
Static	16 (57.1)	52 (45.2)	
Disagree	0 (0.0)	6 (5.2)	
I cannot interact with the children because I am overburdened.			0.00**
Agree	3 (10.7)	46 (40.0)	
Adjusted residual‡	-2.93**	2.93**	
Static	22 (78.6)	65 (55.7)	
Adjusted residual‡	2.22*	-2.22*	
Disagree	3 (10.7)	4 (4.3)	
Adjusted residual‡	1.32	-1.32	

†Chi-square test or Fisher's exact test. ** $p < 0.01$. ‡Adjusted residual: We conducted residual analysis to explore which cells contribute to the significant association if we found significant differences using the chi-square test or Fisher's exact test in the three groups. Usually, adjusted residual of ± 1.96 < and ± 2.58 < indicate $p < 0.05$ and $p < 0.01$.

amount of parenting that is required can cause parents to experience negative emotions toward parenting, parental burnout, or abusive behavior toward their children. In fact, many international agencies such as the World Health Organization warned that children and their families were at risk due to increased parenting stress and violence against children during the COVID-19 pandemic (*30,31*). In this study, one-third of fathers reported feeling tired due to parenting (35.7%) or did not have enough free time (42.9%). Tiredness and dissatisfaction with free time can easily trigger negative emotions toward parenting or parental burnout (*25,32*). Moreover, parents often take responsibility for parenting and their job in parallel at home during the COVID-19 pandemic. Fathers need to draw boundaries between parenting and their work with good balance. However, this is not easy for fathers to do because many fathers are inexperienced at balancing parenting and their work and may not have efficient strategies unlike mothers (*33*). Thus, it is important to support fathers so that paternal involvement does not turn into heavy parenting burdens.

Mothers who answered that their frequency of daily care for children decreased were much fewer than mothers who answered that their frequency increased or remained static. In other words, mothers still had an increased parenting responsibility during the COVID-19 pandemic. This finding may complement previous studies (*34,35*). The burden of households or parenting inescapably increases due to staying at home, and it is likely to be borne mainly by mothers. As a result, maternal parenting did not reduce even if fathers had cooperated more than they did before the COVID-19 pandemic. Additionally, more than half of the mothers were employed, and approximately 40% agreed that they felt tired due to parenting or could not interact with their children because they were overburdened. Caregivers often adjust their time or work according to their family's needs, and consequently, they can experience more work-related adjustments and pressure compared to before the lockdown (*36-38*), all of which can lead to exhaustion. The longer the COVID-19 pandemic continues, the higher the risk of developing maternal mental health problems or burnout. Maternal mental health problems or burnout can lead to maternal abusive behavior toward children and mental health problems in children (*7,39,40*). In fact, some mothers answered that they displayed abusive behavior toward their children after the COVID-19 pandemic, even though they did not before the pandemic. Therefore, we recommend that support for mothers be provided urgently.

Based on the findings of this study, we have identified some implications for practice. We recommend that the support provided by family support workers to both fathers and mothers should reflect the following changes in parenting that resulted from the COVID-19 pandemic. Some fathers felt tired because of parenting or did not have enough free time. Previous studies reported that paternal resilience is associated with parent-child relationship closeness, and that parents who had good parent-child relationships had reduced parental burnout scores during the COVID-19 pandemic (*35,41*). In other words, it may be possible to lighten the paternal burden of parenting by helping fathers to have good parent-child relationships. Family support workers should assess father-child relationships and provide appropriate support for fathers. Moreover, a previous study showed that fathers who had good relationships with other fathers during the COVID-19 pandemic felt that this had a positive impact on their mental health (*42*). Therefore, it is also important to help fathers

find opportunities for recreational activities during parenting. Family support workers should provide fathers with the opportunity to interact with peers in line with current COVID-19 measures and policies, such as online or outdoor meetings, to maintain involvement with their young children without negative emotions toward parenting.

Some mothers felt tired due to parenting or could not interact with their children because they were overburdened. Therefore, family support workers should provide mothers with support to reduce their heavy burden of continuous parenting. Mothers have lost the opportunity to seek support to prevent coronavirus infections. It is pointed out that limited access to social support can lead to parental burnout or inadequate parenting behavior (*20,43,44*). We recommend that family support workers develop a new approach to parenting support so that mothers can easily receive support without worrying about being infected with COVID-19. Family support workers may also provide parenting support services using online platforms, wherein mothers can consult with family support workers about parenting. Concurrently, it is important to train specialists in parenting support because sufficient staffing is even more necessary to help mothers than it was before the COVID-19 pandemic. This will facilitate healthy parenting, healthy growth in children, and a healthy adjustment to the COVID-19 crisis.

This study has several limitations. First, there was a lack of sufficient sample size in a limited zone and an imbalance between the numbers of fathers and mothers. Second, this study is based on parental self-evaluation, and some answers may differ from actual situations. The possibility of recall bias cannot also be excluded. Future studies would benefit from a larger sample size and should include parents from various backgrounds. Additionally, future studies should objectively evaluate parental perceptions and involvement with young children and conduct longitudinal observations.

Conclusions

During the COVID-19 pandemic, approximately half of the fathers experienced positive changes in parenting, while approximately 40% of mothers experienced negative changes. It is suggested that family support workers should provide support for parenting by both fathers and mothers. This would contribute to young children's healthy growth and development despite a public health crisis.

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BRIEF REPORT

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Investigation of the use of PCR testing prior to ship boarding to prevent the spread of SARS-CoV-2 from urban areas to less-populated remote islands

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Abstract: Preventing coronavirus disease (COVID-19) outbreaks and the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from urban areas to less-populated remote islands, many of which may have weak medical systems, is an important issue. Here, we evaluated the usefulness of pre-boarding, saliva-based polymerase chain reaction (PCR) screening tests to prevent the spread of SARS-CoV-2 from Tokyo to the remote island of Chichijima. The infection rate on the island during the study period from September 1, 2020 to March 21, 2021 was 0.015% (2/13,446). Of the 8,910 individuals tested before ship boarding, seven tested positive for COVID-19 (PCR tests of saliva samples). One was confirmed positive by subsequent confirmatory nasopharyngeal swab testing. Based on the testing results, positive cases were denied entry onto the ship to prevent the spread of COVID-19 from Tokyo to Chichijima. This study demonstrated that implementing pre-boarding PCR screening tests is a useful strategy that can be applied to other remote islands with vulnerable medical systems.

***Keywords*:** pre-boarding screen, COVID-19, saliva-based polymerase chain reaction

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in more than 800,000 deaths globally between December 2019 and August 2020. Human-to-human transmission readily occurs, which has led to the spread of COVID-19 to almost all continents of the world. The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on January 30, 2020 and a pandemic on March 11, 2020. Since then, the high rates of SARS-CoV-2 transmission have been of great concern, as rapid human-to-human transmission may lead to COVID-19 cluster formation. The first outbreak of COVID-19 on a cruise ship was reported on the Diamond Princess cruise ship, wherein a passenger who had disembarked from Hong Kong tested positive for COVID-19 on February 1, 2020. The ship, with 3,711 passengers and crew members, was quarantined immediately after reaching Japanese waters on February 3, 2020. Over the next month, more than 700 people on board were infected, and for weeks, the ship was the site of the largest outbreak outside of China (*1*).

This incident suggests that spending long periods with infected individuals in closed spaces increases the risk of infection significantly (*2*). Outbreaks occur easily on vessels due to individual's proximity and a high proportion of older people, who tend to be more vulnerable to the disease.

Although a high risk of transmission arose from the episode of the Diamond princess, there are areas and islands where water liners are the only possible means to reach the area. Therefore, in the case of these islands that can only be reached by ship, it is necessary to consider quarantine measures, such as isolating COVID-19-positive cases before boarding. Chichijima is the largest island in the Ogasawara Islands, located about 1,000 km south of Tokyo and inhabited by approximately 2,100 residents (*3*).

The only way to reach Chichijima is by ship, taking approximately 24 h from Tokyo. (Figure 1, Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=49*). The island has only one clinic, which is not fully equipped to manage severe cases of COVID-19. Individuals on the island suspected of having a SARS-CoV-2 infection (persons with symptoms such as fever and cough) undergo rapid lateral flow antigen testing, which requires a nasopharyngeal swab and no special equipment. Subsequently, positive individuals are transferred to a specified hospital in Tokyo. In the case of negative individuals who are strongly suspected of having SARS-CoV-2 infection, specimens are transported to the mainland for testing by polymerase chain reaction (PCR). Suspected cases who test positive are transferred to the mainland using Self Defense Force helicopters to prevent the spread of the virus. To reduce the risk of outbreaks and keep the island safe from the pandemic, it is necessary to screen passengers traveling from the mainland to Chichijima Island using PCR tests prior to boarding.

Following this concept, the Tokyo Metropolitan Government conducted SARS-CoV-2 PCR testing using the saliva samples of all passengers who planned to board a regular ship from Tokyo to Chichijima between September 1, 2020 and March 31, 2021. Studies have evaluated the epidemiological and laboratory findings of SARS-CoV-2, the public health response to SARS-CoV-2 in Canada, and telemedicine in quarantined areas using simulation models in Australia (*4,5*). However, to our knowledge, this is the first study to evaluate the strategies for identifying infected individuals before they travel from large urban cities, where the community spread of SARS-CoV-2 is ongoing, to remote islands. Although studies on screening tests at airport quarantine stations have been conducted, this study elucidated the importance of extensive PCR testing of individuals with suspected SARS-CoV-2 infection who are asymptomatic, thereby facilitating quarantine measures.

Materials and Methods

Data collection

Saliva collection kits were distributed free of charge to those traveling to Chichijima from the mainland one week before embarking. Tests were not conducted among people traveling from Chichijima to the mainland. Saliva collection, a non-invasive and simple procedure, could be performed by the passengers themselves, with a small exposure risk to the person collecting the sample (*6*). Saliva samples self-collected at least 24 h prior to boarding were used for the screening test. All room temperature specimens were sent by post to the SB Coronavirus Inspection Center Corp. (Tokyo, Japan), a diagnostic company, after which the SARS-CoV-2 Direct Detection RT-qPCR Kit (Takara Bio Inc., Shiga, Japan) was used for testing per the manufacturer's instructions (*7*). We collected written questionnaires from those who agreed to have their saliva samples tested; and the questionnaires contained several questions to ascertain their general characteristics. Those who did not provide consent

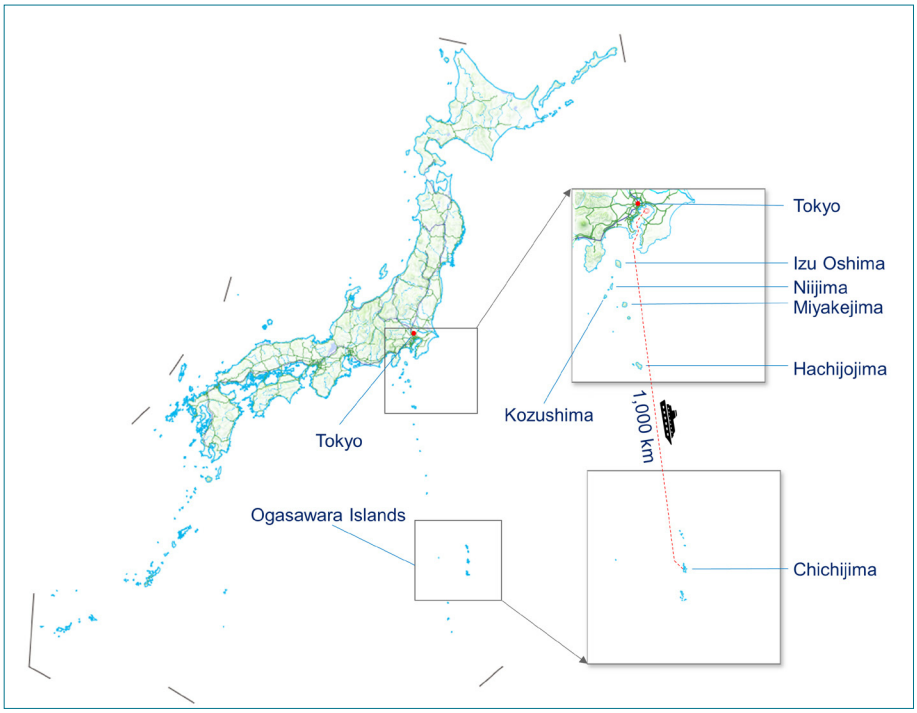

Figure 1. Location of Chichijima and the route from Tokyo to Chichijima.

were not included in the survey. Vaccinations were not yet available in Japan during the study period. During the seven-month study period, 34 round trips were conducted. Among the 11,372 passengers attempting to board the ship, 8,910 agreed to undergo PCR testing before boarding (testing rate, 78.4%) (Figure 2).

Ethics approval

Prior to testing, all saliva samples were processed to avoid identifying specific individuals and recovering personal data. Participants had the opportunity to refuse to participate in the study through the website. This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval number: NCGM-G-003678-00, date of approval: August 5, 2020). The study was in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation or counts (percentages). Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results and Discussion

As of March 2021, among the seven individuals who tested positive for COVID-19 during the screening, one was confirmed positive in a subsequent confirmatory PCR test at a COVID-19 designated hospital in Tokyo; the remaining six tested PCR-negative for COVID-19 with the confirmatory PCR tests performed two to three days later. To understand the discrepancies between the results of the screening and confirmatory tests, we checked the cycle threshold (Ct) values of the PCR tests and found that all values were at the borderline of the detection limit (Ct < 40.0). This suggests that the cases were either false positives or that the number of viral copies was below the lower limit of detection at the time of the confirmatory test. Hence, these seven individuals did not board the vessel.

As of March 1, 2021, only two confirmed cases of COVID-19 had been reported on Chichijima Island. The first was a passenger who had a negative PCR test result at the time of boarding. As there was a 7-day interval between pre-boarding screening and diagnosis, the patient must have been in the "window period" at the time of screening. In the second case, a resident of the island was in close contact with the aforementioned passenger and was infected while residing on the island. During this period, Ogasawara Village required all visitors to record their temperature, wear a mask, and restrict large groups of visitors. For those who wished to consult the doctor for symptoms of acute infection, the doctor conducted medical interviews and antigen tests. If the antigen test results were positive, the patients were transported from Chichijima to Tokyo. In addition, the number of people on board the ships was reduced by 30-50%, and the ships were regularly ventilated and sterilized. Disinfectants were also made available in

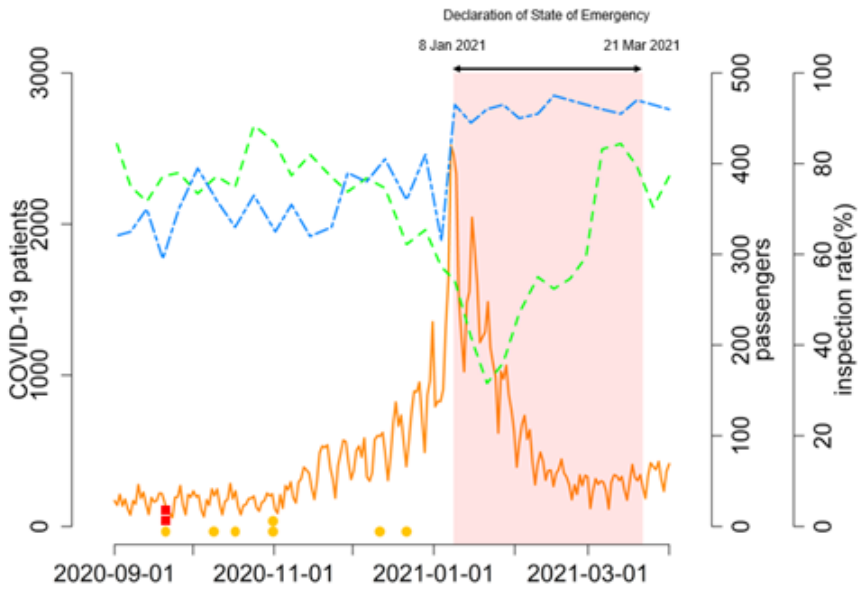

Figure 2. The orange line indicates the coronavirus disease (COVID-19) cases that occurred in Tokyo between September 1, 2020 and March 31, 2021. The green line indicates the number of passengers traveling from Tokyo to Chichijima, and the blue line indicates the testing rate of saliva samples by polymerase chain reaction (PCR) before boarding the vessel. The red squares indicate COVID-19 cases that occurred in Chichijima, and the orange circles indicate patients who tested positive for COVID-19 using saliva samples subjected to PCR prior to boarding. The period of declaration of a state of emergency is indicated by the orange block.

restaurants, employees wore masks and gloves when serving customers, and seats were regularly wiped and disinfected.

The incidence of COVID-19 among residents and visitors was 0.015% (2/13,446) (Figure 3). Although 24 h are required to reach Chichijima, and there is a high risk of infection on board, the percentage of infected people in Chichijima was relatively low compared with that of other islands in Tokyo. Furthermore, the cumulative number of infected persons and the ratio of infected persons to the total population in Tokyo during the study period were 100, 172, and 0.71%, respectively, with the infection rate in Chichijima being much lower than that in Tokyo (*8,9*). Among the 8,910 individuals tested before boarding the ship during this study, seven tested positive with saliva-based PCR testing and one with subsequent nasopharyngeal swab testing. The low rate of infection may imply that the low number of SARS-CoV-2-positive people in Japan might have led to this result. However, another remote island, which had direct flights from Tokyo and no special quarantine system, reported several cases of COVID-19 daily (*10*). On an island as remote as Chichijima, preventing COVID-19 outbreaks is imperative. PCR testing before boarding the vessel to Chichijima may be a crucial screening measure in preventing those outbreaks.

Data pertaining to the general characteristics of the participants are presented in Table 1. Interestingly, even during the pandemic, the major reason for boarding was tourism (48.2%), followed by business (33.1%), residence (11.4%), and homecoming (5.4%). There were more men (n = 5,836) than women (n = 3,021), and the average age was 43.3 ± 16.7 years. The average body temperature at the time of examination was 36.2 ± 0.4oC. There were 76 (0.85%) participants who reported symptoms on the day before boarding, but they all tested negative for COVID-19.

Cruise ships carry a large number of people in confined spaces with relatively higher homogeneous mixing over a period of time that is longer than that for any other mode of transportation. Thus, cruise ships present a unique environment for the transmission of human-to-human infections, including SARS-CoV-2. Several outbreaks of diseases on cruise ships have been reported in the past. An outbreak of a severe acute respiratory infection occurred on a cruise ship off Brazil in February 2012 that caused 16 hospitalizations and one death (*11*). In May 2009, a dual outbreak of the influenza A virus subtype H1N pandemic (swine flu) and influenza A (H3N2) occurred on a cruise ship. Among the 1,970 passengers and 734 crew members, 82 (3.0%) were infected with the swine flu, and 98 (3.6%) were infected with the influenza A (H3N2) virus (*12*).

Although pre-boarding PCR testing was successful, as was evident from the small number of COVID-19 cases reported on the island, the following study limitations should be considered. First, since the pre-boarding PCR test was voluntary, only 78.4% of the passengers agreed to undergo the test. The reasons for not undergoing the test were not clear, but fear of being identified as infected and not being allowed to board the ship may have been one major reason. It is noteworthy that during the state of emergency (January 8, 2021 to March 21, 2021), the percentage of pre-boarding PCR testing increased significantly from 71.8% to 92.3% (Student's t-test, p = 0.003) (Figure 2), indicating that the state of emergency declaration may have led to behavioral changes. Second, the sensitivity and specificity of saliva tests have been reported to be 86.4% (95% confidence interval [CI]: 82.8%-89.4%) and 97.0% (95% CI: 95.0%-98.3%), respectively (*13*). Moreover, as the specimens were self-collected, there was a risk of improper collection, which may have

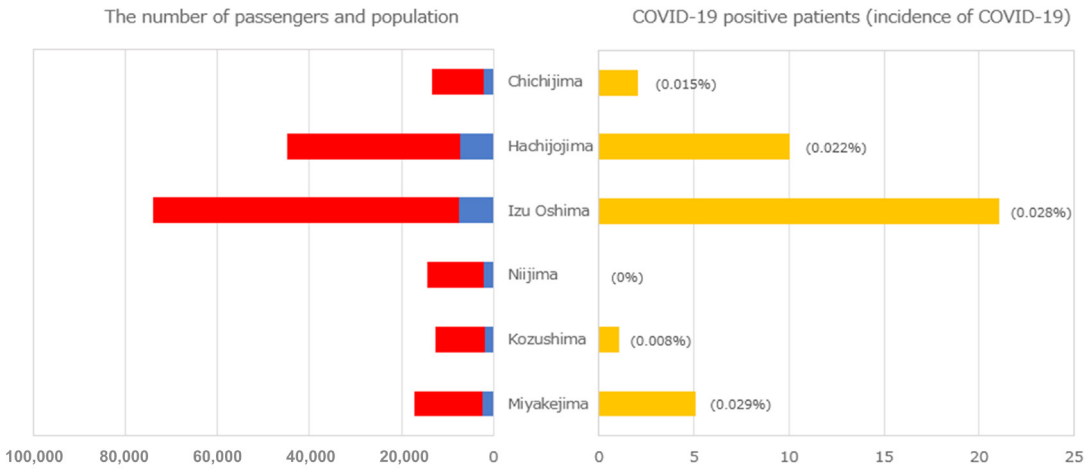

Figure 3. The left figure shows the population and passenger numbers. The blue and red bars indicate the population and passengers, respectively. The right figure shows the number of COVID-19-positive patients and the incidence of COVID-19. The incidence of COVID-19 was calculated as follows: (number of COVID-19 positive cases/total number of passengers and the population) × 100%.

Table 1. Characteristics of the study participants

Characteristics	Values
Total number of passengers expected to travel from Tokyo to Chichijima*	11,372
Total number of passengers who responded to the screening test	8,910
Response rate (%)	78.4
Total number of passengers who boarded the ship†	11,294
Age (years), mean ± SD‡	43.3 ± 16.7
Sex, *n* (%)	
Male	5,836 (65.5)
Female	3,021 (33.9)
Not available	53 (0.6)
Body temperature (°C), mean ± SD	36.2 ± 0.4
Symptoms, *n* (%)	
Cough and phlegm	66 (0.7)
Feeling of fatigue	11 (0.1)
Olfactory impairment	2 (0.02)
Dysgeusia	2 (0.02)
No symptom	8,702 (97.7)
Reasons for visiting the island, *n* (%)	
Residence	1,012 (11.4)
Retreat	477 (5.4)
Business	2,946 (33.1)
Sightseeing	4,299 (48.2)
Others	286 (3.2)

*All prospective passengers, except those aged < 6 years, were considered for testing. †Refers to the actual number of passengers on board, including those aged < 6 years. This included the passengers who canceled their boarding and those who were not allowed to board because they tested positive with the screening test. ‡SD, standard deviation.

increased the number of false negative PCR results. Third, individuals in the early stages of COVID-19 might have been in the "window period" (*14*), wherein the tests might have yielded a negative result. Fourth, no follow-up using a standard PCR was performed 3 or 7 days after arrival on the island to ascertain the number of passengers who may have been in the "window period" or to validate the saliva-based PCR tests. Finally, it is possible that the medical system failed to identify all COVID-19 cases. However, adequate antigen testing can be performed in Chichijima, and when necessary, specimens can be sent to hospitals in central Japan for PCR testing, even if the results of the antigen tests are negative. This approach may be effective in identifying all COVID-19 cases on the island. While there are no simple actions to address the above limitations, it is crucial to educate people that false negative PCR test results are possible. Moreover, standard precautions for COVID-19, including reducing the number of passengers on board by 30% to 50%, regular ventilation and sterilization of the ship, provision of disinfectants in restaurants, wearing of gloves and masks by employees during contact with customers, and disinfection of seats during the cruise, are continuously implemented.

In conclusion, the implementation of PCR screening prior to boarding prevented seven suspected positive cases from visiting the remote island, thus minimizing the number of infected people and the spread of infection on the island. During the study period, many outbreaks occurred on other islands that were visited by passengers from heavily infected areas in Tokyo. In particular, on remote islands where it takes a long time to reach appropriate medical care facilities, the prevention of outbreaks is crucial. Our findings indicate that for islands with vulnerable medical systems, PCR screening prior to boarding should be considered to prevent infected individuals from visiting the island.

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BRIEF REPORT
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Exploratory study on relative dose intensity and reasons for dose reduction of adjuvant CAPOX therapy in elderly patients with colorectal cancer

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Abstract: Capecitabine plus oxaliplatin, CAPOX, therapy is one of the standardized options for adjuvant chemotherapy for colorectal cancer, but the efficacy and the safety of CAPOX in elderly patients are unclear. In this study, we investigated the relative dose intensity (RDI) and reasons for dose reduction in patients over the age of 70 (elderly group) (n = 12) and those under the age of 70 (non-elderly group) (n = 24) receiving adjuvant CAPOX therapy for colorectal cancer. The median RDIs were 71.1% in the elderly group and 67.9% in the non-elderly group for oxaliplatin (p = 0.416), and 81.6% and 86.4% for capecitabine (p = 0.166), respectively. The rate of peripheral neuropathy which was the reason for dose reduction of oxaliplatin was approximately 4.5-fold higher in the non-elderly group than in the elderly group. In addition, hematologic toxicity was the most common reason for dose reduction at 50.0% in the elderly group. The results of this study suggested that a similar therapeutic intensity can be maintained in elderly patients relative to non-elderly patients by appropriate dose reduction and discontinuation of drug treatments. Elderly patients are more susceptible to hematologic toxicity than to peripheral neuropathy.

Keywords: oxaliplatin, over the age of 70, therapeutic intensity, peripheral neuropathy, hematologic toxicity

Introduction

Cancer has been the leading cause of death in Japan since 1981. According to the latest cancer statistics from the Center for Cancer Control and Information Services, National Cancer Center, colorectal cancer was the most common cancer in 2017, and its age-adjusted incidence rate in people over the age of 70 was 59% in 2015, accounting for more than half of the total incidence rate (*1*).

Surgery and adjuvant chemotherapy are regarded as the standard treatment for resectable colorectal cancer. CAPOX therapy, a combination of capecitabine and oxaliplatin, has been shown to be superior to fluorouracil (FU) + levofolinate calcium (*l*-LV) therapy in terms of disease-free survival (DFS) (*2*). It has become one of the standardized options for adjuvant chemotherapy for colorectal cancer in Japan.

Adjuvant chemotherapy with an FU-based regimen has been shown to be effective regardless of age; however, the results of clinical trials evaluating the efficacy of the combined use of oxaliplatin are still controversial (*3-5*), and consistent results have not been obtained (*6*). Furthermore, peripheral neuropathy arises in a dose-dependent manner when oxaliplatin is used in combination (*7,8*). There are only a few reports of adverse events in patients over the age of 70 that have been investigated to date, and they are often excluded from clinical trials because of worse performance status or complications. The Clinical Practice Guidelines of Cancer Drug Therapies for the Elderly (*9*) stipulate that "adjuvant chemotherapy may be considered for elderly patients with good performance status and organ function and no serious complications", but the efficacy and the safety of the CAPOX therapy in patients over the age of 70 have not been clarified.

In this study, we investigated the relative dose intensity (RDI) and reasons for dose reduction in patients over the age of 70 and those under the age of 70 receiving adjuvant CAPOX therapy for colorectal cancer.

Patients and Methods

Patients

Patients over the age of 18 who started CAPOX therapy as adjuvant chemotherapy for colorectal cancer at the Center Hospital of the National Center for Global

Health and Medicine (NCGM) between January 2018 and August 2019 were included. Surgery was performed on all patients within 8 weeks. Of these patients, those who met the criteria of white blood cells ≥ 3,000/mm^3, neutrophils ≥ 1,500/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 8.0 mg/dL, total bilirubin ≤ 1.5 mg/dL, and serum creatinine ≤ 1.5 mg/dL at the start of treatment were included. Other eligibility criteria included an Eastern Cooperative Oncology Group Performance Status of 0/1. Patients with known peripheral neuropathy were excluded.

Methods

CAPOX therapy consisted of 8 courses of treatment with each course as a 21-day cycle, administering 130 mg/m^2 oxaliplatin on day 1 and 2,000 mg/m^2 capecitabine per day from after dinner on day 1 to after breakfast on day 15.

A retrospective survey was conducted based on electronic medical records. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE ver.5.0). The RDI was calculated as (Actual total dose/Actual total administration period)/(Planned total dose/Planned total administration period) × 100 (%). Based on the Guidelines for the Treatment of Colorectal Cancer, "elderly" was defined as over the age of 70. Patients over the age of 70 (elderly group) was compared with those under the age of 70 (non-elderly group).

Baseline characteristics of patients, course of treatment, RDI (%), reasons for dose reduction and discontinuation of oxaliplatin, and reasons for dose reduction of capecitabine were investigated.

Statistical analysis

The Mann-Whitney *U* test was used to compare quantitative data, and the chi-square test or the Fisher's exact test was used to compare qualitative data. In all cases, $p < 0.05$ was considered a statistically significant difference. IBM SPSS® Statistics ver.24 was used for all statistical analyses.

Ethical conduct of the study

This study was conducted with the approval of the Ethical Review Committee of NCGM (Approval number: NCGM-G-003546-01), in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and paying the utmost attention to the protection of personal information.

Results and Discussion

Baseline characteristics of the study patients

The baseline characteristics of the 36 patients are shown in Table 1. The median age of the 12 elderly patients and the 24 non-elderly patients was 74.0 and 52.0, respectively. Laboratory data prior to the start of treatment indicated that hemoglobin and albumin were significantly lower in the elderly than in the non-elderly group ($p = 0.026$ and 0.022, respectively).

Course of treatment

The courses of treatment for the 36 patients are shown in Figure 1. In total, 69.4% of the patients (25/36) completed the 8 courses. The rate of treatment completion in the elderly group ($n = 12$) and the non-elderly group ($n = 24$) was 58.3% (7/12) and 75.0% (18/24), respectively. The reasons for failure to complete treatment in the elderly-vs-non-elderly groups were recurrence in 1 and 4 patients; concomitant other diseases or progression of other diseases such as lung cancer in 4 and 0 patients; financial considerations in 0 and 1 patient; and a personal decision in 0 and 1 patient, respectively.

Relative dose intensity (RDI) of CAPOX

The median RDIs in the elderly and non-elderly patients who completed the 8 courses are shown in Figure 2. The RDIs of oxaliplatin were 71.1% and 67.9%, respectively (not significant, $p = 0.416$) and the RDIs of capecitabine were 81.6% and 86.4%, respectively (also not significant, $p = 0.166$).

Reasons for dose reduction or discontinuation of oxaliplatin and capecitabine

The reasons for dose reduction and discontinuation of oxaliplatin are shown in Table 2 and the reasons for dose reduction of capecitabine are shown in Table 3. The rate of peripheral neuropathy which was the reason for dose reduction of oxaliplatin was 8.3% (1/12) in the elderly group but approximately 4.5-fold higher in the non-elderly group (37.5%; 9/24). All patients discontinuing oxaliplatin due to peripheral neuropathy were in the non-elderly group, accounting for 29.2% (7/24), with a median number of 6 oxaliplatin courses. In addition, in the elderly group, the most common reason for dose reduction of oxaliplatin was hematologic toxicity in 50.0% of the patients (6/12).

Discussion

The actual condition of treatment in patients over the age of 70 who were treated with adjuvant CAPOX therapy for colorectal cancer at NCGM is reported here. The rate of treatment completion was lower in the elderly group than in the non-elderly group, but not all reasons for failure to complete treatment were due to adverse events. In addition, there was no difference in

Table 1. Baseline characteristics of patients

Characteristic	Elderly (n = 12)	Non-Elderly (n = 24)	P value
Age, years			
Median (Range)	74.0 (70.0-77.0)	52.0 (27.0-67.0)	
Sex			0.451
Male	7 (58.3%)	17 (70.8%)	
Female	5 (41.7%)	7 (29.2%)	
Body surface area, m^2			
Average ± SD	1.60 ± 0.167	1.70 ± 0.174	0.128
ECOG-PS			1.000
0/1/2/3/4	9/3/0/0/0	18/6/0/0/0	
Laboratory data			
White blood cell ($\times10^3/mm^3$)	5.73 ± 1.04	5.74 ± 2.13	0.728
Neutrophil ($\times10^3/mm^3$)	3.71 ± 1.21	3.64 ± 1.74	0.497
Hemoglobin (g/dL)	11.2 ± 2.50	12.8 ± 1.84	0.026
Platelet ($\times10^4/mm^3$)	27.2 ± 8.68	29.1 ± 12.4	0.753
Total bilirubin (mg/dL)	0.555 ± 0.202	0.546 ± 0.277	0.908
Serum creatinine (mg/dL)	0.754 ± 0.207	0.798 ± 0.196	0.361
Albumin (g/dL)	3.92 ± 0.397	4.23 ± 0.493	0.022
Site			
Ascending colon	4 (33.3%)	1 (4.17%)	
Transverse colon	2 (16.7%)	0 (0%)	
Descending colon	0 (0%)	3 (12.5%)	
Sigmoid colon	3 (25.0%)	6 (25.0%)	
Rectum	1 (8.33%)	10 (41.7%)	
Cecum	2 (16.7%)	2 (8.33%)	
Appendix vermiformis	0 (0%)	2 (8.33%)	
Stage			
IIIa	2 (16.7%)	5 (20.8%)	
IIIb	6 (50.0%)	9 (37.5%)	
IIIc	1 (8.33%)	4 (16.7%)	
IV (liver metastasis)	3 (25.0%)	4 (16.7%)	
unclear	0 (0%)	2 (8.33%)	

SD: standard deviation, ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

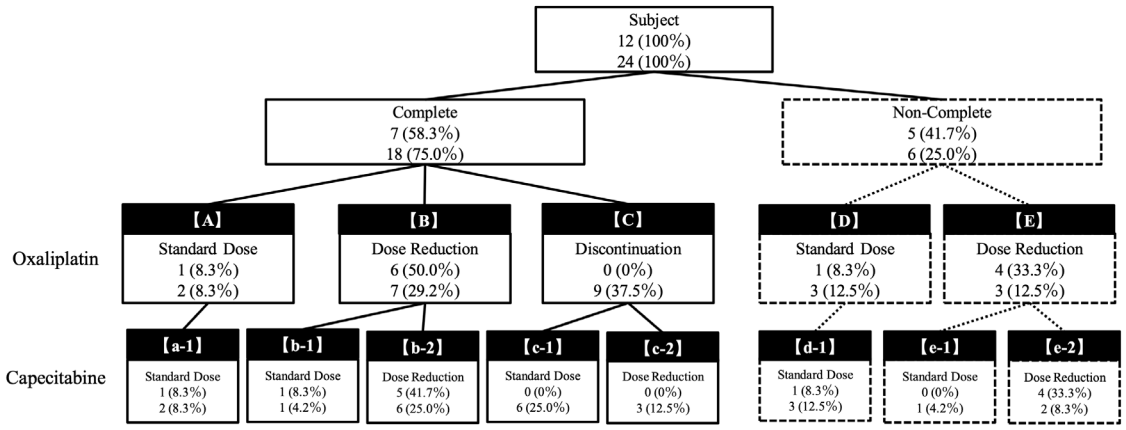

Figure 1. Course of treatment. Upper row; Elderly, Lower row; Non-Elderly. **(A)**: Oxaliplatin Standard Dose, Complete. **(B)**:Oxaliplatin Dose Reduction, Complete. **(C)**:Oxaliplatin Discontinuation, Complete. **(D)**:Oxaliplatin Standard Dose, Non-Complete. **(E)**:Oxaliplatin Dose Reduction, Non-Complete. **(a-1)**:(A) and Capecitabine Standard Dose, Complete. **(b-1)**:(B) and Capecitabine Standard Dose, Complete. **(b-2)**:(B) and Capecitabine Dose Reduction, Complete. **(c-1)**:(C) and Capecitabine Standard Dose, Complete. **(c-2)**:(C) and Capecitabine Dose Reduction, Complete. **(d-1)**:(D) and Capecitabine Standard Dose, Non-Complete. **(e-1)**:(E) and Capecitabine Standard Dose, Non-Complete. **(e-2)**:(E) and Capecitabin Dose Reduction, Non-Complete.

RDIs between the two groups for either oxaliplatin or capecitabine in patients who completed the 8 courses. These results suggest that it is possible to complete treatment while maintaining the therapeutic intensity even in patients over the age of 70. On the other hand, discontinuation of treatment due to concomitant other diseases or progression of other diseases was more frequent in the elderly group, suggesting that it is necessary to intervene with elderly patients, paying attention not only to the occurrence of adverse

events but also to the complications that may require discontinuation of treatment.

Anemia, hypoalbuminemia, hypomagnesemia, and habit of alcohol consumption are known to be risk factors for peripheral neuropathy, especially in oxaliplatin-treated patients (*10*). In the present study, hemoglobin and albumin levels prior to the start of treatment were significantly lower in the elderly group. In addition, serum magnesium levels were often not included in the laboratory data prior to the start of treatment, and there were cases in which there were no medical records regarding alcohol consumption. Therefore, characteristics of the patients in this study were insufficient to confirm the risk factors for peripheral neuropathy. The hemoglobin and albumin levels suggest that the risk of peripheral neuropathy is high in the elderly group. However, the effects of peripheral neuropathy were lower in the elderly group than in the non-elderly group in the results of this survey; thus, we investigated the effects of age on peripheral neuropathy.

There have been several reports of the age-specific risks of oxaliplatin-induced peripheral neuropathy. A study comparing patients with colorectal cancer

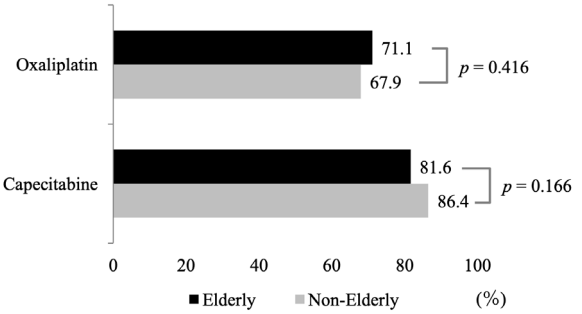

Figure 2. Median relative dose intensities (RDIs) in patients completed 8-courses. The median RDIs of oxaliplatin were 71.1% in the elderly and 67.9% in the non-elderly ($p = 0.416$). The RDIs of capecitabine were 81.6% and 86.4%, respectively ($p = 0.166$).

Table 2. Reasons for dose reduction and discontinuation of oxaliplatin

Reason	Dose Reduction									Discontinuation							
	Elderly (n = 12)				Non-Elderly (n = 24)				P value	Elderly (n = 12)				Non-Elderly (n = 24)			
	All Grade		Grade ≥ 3		All Grade		Grade ≥ 3			All Grade		Grade ≥ 3		All Grade		Grade ≥ 3	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)		No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hematologic toxicity	6	(50.0)	2	(16.7)	6	(25.0)	3	(12.5)	0.157	0	(0)	0	(0)	2	(8.3)	1	(4.2)
Neutropenia	3	(25.0)	0	(0)	5	(20.8)	3	(12.5)	1.000	0	(0)	0	(0)	1	(4.2)	1	(4.2)
Thrombocytopenia	5	(41.7)	2	(16.7)	3	(12.5)	0	(0)	0.086	0	(0)	0	(0)	1	(4.2)	0	(0)
Non-Hematologic toxicity	4	(33.3)	2	(16.7)	14	(58.3)	5	(20.8)	0.157	0	(0)	0	(0)	7	(29.2)	2	(8.3)
Peripheral neuropathy	1	(8.3)	0	(0)	9	(37.5)	2	(8.3)	0.115	0	(0)	0	(0)	7	(29.2)	2	(8.3)
Anorexia	2	(16.7)	1	(8.3)	1	(4.2)	0	(0)	0.253	0	(0)	0	(0)	0	(0)	0	(0)
Diarrhea	1	(8.3)	1	(8.3)	4	(16.7)	2	(8.3)	0.646	0	(0)	0	(0)	0	(0)	0	(0)
Nausea	0	(0)	0	(0)	2	(8.3)	0	(0)	0.543	0	(0)	0	(0)	0	(0)	0	(0)
Malaise	0	(0)	0	(0)	1	(4.2)	1	(4.2)	1.000	0	(0)	0	(0)	0	(0)	0	(0)
Infection	1	(8.3)	0	(0)	1	(4.2)	0	(0)	1.000	0	(0)	0	(0)	0	(0)	0	(0)

There is some overlapping. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. The worst grade considered at least possibly related to treatment is given. The *P* values are for the differences between the groups for all grades.

Table 3. Reasons for dose reduction of capecitabine

Reason	Elderly (n = 12)				Non-Elderly (n = 24)				P value
	All Grade		Grade ≥ 3		All Grade		Grade ≥ 3		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Hematologic toxicity	4	(33.3)	2	(16.7)	5	(20.8)	3	(12.5)	0.443
Neutropenia	1	(8.3)	0	(0)	4	(16.7)	3	(12.5)	0.646
Thrombocytopenia	3	(25.0)	2	(16.7)	2	(8.3)	0	(0)	0.307
Non-Hematologic toxicity	6	(50.0)	2	(16.7)	7	(29.2)	3	(12.5)	0.281
Anorexia	1	(8.3)	0	(0)	1	(4.2)	0	(0)	1.000
Diarrhea	1	(8.3)	1	(8.3)	4	(16.7)	2	(8.3)	0.646
Hand-foot syndrome	3	(25.0)	1	(8.3)	2	(8.3)	1	(4.2)	0.307
Infection	1	(8.3)	0	(0)	0	(0)	0	(0)	0.333

There is some overlapping. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. The worst grade considered at least possibly related to treatment is given. The *P* values are for the differences between the groups for all grades.

aged 50 to 68 years with those over the age of 69 who were treated with adjuvant chemotherapy or first-line treatment for metastatic disease reported no age-associated statistically significant difference in acute or chronic peripheral neuropathy (*11*). On the other hand, in a study of patients with colorectal cancer who were treated with adjuvant chemotherapy, the risk of peripheral neuropathy was reported to be higher in patients over the age of 70 than in those aged 66 to 69 years (*12*). It has also been reported that the duration of peripheral neuropathy was longer in patients under the age of 60 than in those over the age of 60 (*10*). Thus, there is no consensus on the risks of oxaliplatin-induced peripheral neuropathy with respect to age.

The effects of peripheral neuropathy were lower in the elderly group than in the non-elderly group in our study. The reason for this may be due to the effect of hematologic toxicity. In the elderly group, hematologic toxicity was the reason for 50.0% of all cases of oxaliplatin dose reductions. In the elderly, the decline in bone marrow function associated with aging may lead to more severe hematologic toxicity and prolonged recovery (*13*). In the present study, there was no significant difference between the elderly and non-elderly groups in the blood cell counts prior to the start of CAPOX therapy except for the hemoglobin level. This suggests that elderly patients may have been more susceptible to hematopoietic exhaustion due to chemotherapy, and may have experienced less peripheral neuropathy due to dose reduction resulting from hematologic toxicity in response to more severe hematologic toxicity and prolonged recovery before the reduction resulting from peripheral neuropathy.

The limitations of this study include the small number of cases; hence, further research is needed on a larger number of patients. Second, we were unable to evaluate efficacy in terms of overall survival or disease-free survival, because there has been insufficient time since completing adjuvant CAPOX therapy. In addition, it was not possible to retrospectively investigate patient adherence with capecitabine, which is an oral anticancer drug. The RDI for capecitabine was calculated based on the number of prescription days, and the RDI may possibly be even lower in patients with poor adherence. Especially in the elderly, who are often treated by polypharmacy due to chronic diseases, in addition to a decline in activities of daily living and cognitive function (*13*), it is important to ensure adherence in order to maintain the therapeutic intensity of CAPOX therapy. In future, it will be necessary to consider including a survey of adherence.

In conclusion, the results of this study suggested that a similar therapeutic intensity can be maintained in elderly patients relative to non-elderly patients by appropriate dose reduction and discontinuation of drug treatments. Elderly patients are more susceptible to hematologic toxicity than to peripheral neuropathy.

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Conflict of Interest: Y.Y. has received honoraria from Chugai, Taiho, and Nipponkayaku, Japan. The other authors declare that they have no conflicts of interest.

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BRIEF REPORT

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Mental foramen in panoramic radiography can be a reference for discrimination of punched-out lesions in the mandible in patients with symptomatic multiple myeloma: A cross-sectional study

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Abstract: Multiple myeloma (MM) is a hematopoietic malignancy characterized by monoclonal proliferation of plasma cells. MM features bony radiolucencies called punched-out lesions (POLs), which require appropriate diagnosis due to increased risk of surgically-related adverse events. Although dental surgeons can identify dental focal infections (DFIs) in MM patients, the prevalence and characteristics of POLs in the jawbone of MM patients have not been investigated. We examined the prevalence of POLs in the mandible of MM patients, evaluated its relationship with MM International Staging System progression, and examined panoramic radiographs as a diagnostic reference for POLs in a single center in Japan. We identified 98 patients (55 men, 43 women) with a median age of 63 (range, 34 to 91) years. Of these, 18 patients (18.4%) had POLs in the mandible, including two patients in stage I (2/37; 5.4%), six in stage II (6/43; 14.0%), and ten in stage III (10/18; 55.6%). The prevalence of POLs significantly increased with MM stage progression ($p < 0.0001$). POLs confirmed on computed tomography (CT) were also detected on panoramic radiographs. The Hounsfield unit value at the site of POLs was nearly the same or lower than that of the mental foramen. Although the prevalence of POLs in the mandible is low, dental surgeons need to differentiate POLs as radiological findings when examining DFIs in MM patients. Confirmation of POLs in the mandible is possible by CT and panoramic radiography, and the mental foramen is likely to be a reference for discrimination.

***Keywords*:** hematologic malignancy, bone disease, mandible, dental focal infection, panoramic radiography, computed tomography

Introduction

Multiple myeloma (MM), also known as plasma cell myeloma, accounts for 1% of all malignancies and 10-15% of all hematopoietic neoplasms. It is characterized by the monoclonal proliferation of plasma cells that originate from the post-germinal lymphoid B-cell lineage and develop in the bone marrow of progenitor cells following lineage commitment (*1,2*). MM is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction such as hypercalcemia, renal insufficiency, anemia, and bone disease (*1,2*). The osteoclast-activating factor, which is released from myeloma cells, enhances bone resorption, thereby precipitating osteolytic bone disease in more than 80% of MM patients (*2*). Osteolytic bone diseases can result in skeletal and surgically-related adverse events such as severe bone pain, pathological fractures, surgical site infection (SSI), and septicemia (*2-6*). These complications have a negative impact on the patient's quality of life and overall survival. In fact, patients with MM have an increased incidence of bone fractures (43%) and risk of death compared to all patients with malignant bone disease (*7*). In addition, approximately 21% of bone diseases in MM patients are associated with postoperative complications such as abnormal bleeding and SSI (*5*). Therefore, it is important to thoroughly assess bone condition preoperatively in MM patients who plan to receive surgical intervention.

Osteolytic lesions in MM patients show a characteristic radiological feature called punched-out lesions (POLs) (*8*), which are multiple radiolucent lesions of various sizes with well-defined non-sclerotic margins (*8,9*). Dental surgeons have the opportunity to evaluate dental focal infections (DFIs) in the

stomatognathic region, which includes the jawbones, before chemotherapy in patients with hematopoietic malignancies, including MM (*10*), and panoramic radiography is often used in the screening of jawbones (*11*). In addition, tooth extraction may be performed to radically remove DFIs (*10*). Although radiodiagnostic proficiency and experience distinguishing between various diseases are crucial for DFI scrutiny in the jawbones, the prevalence and characteristics of POLs and the diagnostic value of panoramic radiography in MM patients have not yet been thoroughly investigated.

In this context, we conducted a study in a single center in Japan to evaluate the prevalence of POLs in the mandible of symptomatic MM patients to analyze the relationship of POL incidence with MM progression and examine the efficacy of panoramic radiographs as a diagnostic reference for POLs.

Materials and Methods

Study design

We conducted a cross-sectional study using medical records of patients with symptomatic MM who visited the National Center for Global Health and Medicine (NCGM), Tokyo, Japan. The time period of this study spanned from January 2011, when the electronic medical record system was introduced at our hospital, to December 2016, the end date of the study when it was approved by the Ethics Review Committee in July 2017. Patients were considered for inclusion in this study when they were referred from the Division of Hematology to the Department of Oral and Maxillofacial Surgery before undergoing chemotherapy. The prevalence of POLs in the enrolled patients' mandible and skull was investigated by computed tomography (CT). The expression rate of the POLs was then compared. We then evaluated whether panoramic radiographs can be used to confirm the presence or absence of POLs.

We analyzed the relationship between POLs and MM stages. The staging was in accordance with the MM International Staging System (ISS), which reflects the progression of MM. In addition, the bone mineral density of CT-confirmed POLs in the mandible, measured in Hounsfield units (HUs), was further evaluated and compared with that of healthy sites such as the mental foramen and cortical bone. Quality was referred to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (*12*).

The study was conducted according to the tenets of the Declaration of Helsinki (2013 revision) and all investigations were performed according to the protocols that were reviewed and approved by the ethical committee of the NCGM (NCGM-G-002190-01). The requirement for informed consent was waived because of the cross-sectional study design.

Eligibility criteria

Subjects were enrolled using the inclusion and exclusion criteria described below. The inclusion criteria were as follows: *i*) patients who visited the NCGM between January 2011 and December 2016; *ii*) those who were diagnosed with symptomatic MM with mandible involvement confirmed on CT; and *iii*) those who visited the Department of Oral and Maxillofacial Surgery for radiographic screening of the jawbone.

The exclusion criteria were as follows: *i*) patients diagnosed with asymptomatic MM; *ii*) those who had already received a bisphosphonate or a RANK ligand inhibitor (*e.g.*, denosumab) *via* any route for any duration because of the known relationship between these medications and osteonecrosis of the jaw (*13*); *iii*) those who had already undergone tooth extraction at another dental clinic or hospital as part of their oral evaluation before chemotherapy; and *iv*) those who moved to another hospital before undergoing radiographic screening of the jawbone.

Data collection

We procured data of all participating patients from the medical, dental, and nursing records of the NCGM. We noted the following variables: age, sex, diagnosis, MM stage, intraoral findings, subjective symptoms, and radiological findings in the cranial and oral maxillofacial regions, including oral panoramic radiographs and CT at the time of diagnosis.

Evaluation of MM progress

The ISS is based on beta-2 microglobulin and albumin levels. It was introduced in 2005 (*14*) and has since been considered the standard for the initial staging of patients with MM (*15*). This staging system defines three stages with varied prognoses (Table 1). This staging system was used to evaluate the degree of MM progression at the time of jawbone scrutiny.

Mandibular assessment

The mandible is a single large bone that makes up the lower part of the facial skeleton and can be subdivided into seven sites: the alveolus, symphysis, mandibular

Table 1. International staging system for multiple myeloma

MM Stage	Definition	
	β2MG [mg/L]	Alb [g/dL]
I	< 3.5	≥ 3.5
II	Not stage I or III	
III	≥ 5.5	NS

MM, multiple myeloma; β2MG, beta-2 microglobulin; Alb, albumin; NS, no setting.

Table 2. Percentage of punched-out lesions in the skull and the mandible according to the international staging system

Sites	ISS stage			Total	Cochran-Armitage trend test
	I	II	III		
Skull	8/37 (21.6%)	16/43 (37.2%)	18/18 (100%)	42/98 (42.9%)	$p < 0.0001$
Mandible	2/37 (5.4%)	6/43 (14.0%)	10/18 (55.6%)	18/98 (18.4%)	$p < 0.0001$

ISS, international staging system.

body, mandibular ramus, mandibular angle, coronoid process, and subcondylar process (*16*). Using the mandible's morphological classification as a guide, we collated the POLs in the mandible of our subjects using CT. However, since it was difficult to strictly distinguish alveolus POLs from dental infections, the alveolus site was excluded. In this study, POLs were defined as radiolucent lesions in the absence of dental infection. Histopathological examinations were not used to define POLs. Radiolucent lesions that were suspected of having any possibility of association with dental infections based on clinical symptoms and images were not regarded as POLs. The presence or absence of POLs and the site of onset were also evaluated by panoramic radiographs. In addition, we verified whether the mental foramen, a radio-anatomical structure clearly visible on panoramic radiographs, can be used as a reference when distinguishing POLs by measuring the bone mineral density of the mandible, accomplished by setting an ellipse on the horizontal cross-section of the CT screen and calculating the average value in the range of 5 mm^2. The measurement sites of the HU value were the following: *i*) mandibular cortical bone on the healthy side without POLs, *ii*) mental foramen, and *iii*) bone inside the POL.

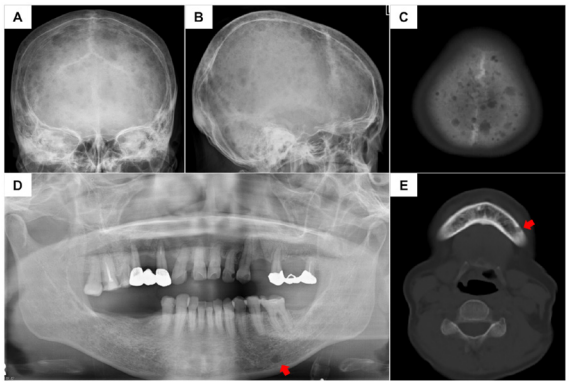

Figure 1. Skull and panoramic radiographs and CT imaging of a 57-year-old woman with MM stage III. (A, B) Skull radiography from the front and side. Various sizes with well-defined multiple POLs in the parietal, frontal, occipital, and temporal bone can be seen. **(C)** Axial CT imaging of the parietal bone showing various sizes with well-defined multiple POLs. **(D)** Panoramic radiograph. A POL with a clear boundary is observed in the mandibular body corresponding to the left second premolar and first molar (arrows). Dental infections were unlikely because they were far from the teeth through healthy bones, and the patient had no deactivated teeth. **(E)** Axial CT imaging of the left mandibular body. A POL with a well-defined, approximately 4-mm × 5-mm internal uniform low-concentration lesion with smooth margins is found in the lateral cortical bone of the left mandibular body (arrows).

Statistical analyses

Data are presented as mean with standard deviation (SD) or median with range for continuous variables and number with percentage for categorical variables. The Cochran-Armitage trend test was used to analyze the incidence of POLs in relation to ISS stage progression. In addition, a one-way analysis of variance for repeated measures followed by Tukey's test for multiple comparisons was used to compare the HU value among the three measurement sites. Statistical analyses were performed using the SAS statistical software package, Version 9.4 (SAS Institute, Cary, NC, USA), and $p < 0.05$ indicated statistical significance.

Results and Discussion

Patient characteristics

Overall, 138 patients with symptomatic MM visited the Department of Oral and Maxillofacial Surgery during the study period. After exclusion, we identified 98 patients (55 men [56.1%], 43 women [43.9%]) with a median age of 63 (range, 34 to 91) years at their first visit to our department. The 98 identified patients were classified according to the ISS; there were 37 patients (37.8%) in stage I, 43 (43.9%) in stage II, and 18 (18.4%) in stage III.

Prevalence of POLs and its correlation with the ISS progress

Of the 98 patients diagnosed with symptomatic MM, 42 (42.9%) and 18 (18.4%) had POLs in the skull and the mandible, respectively (Table 2). Figure 1 shows one of the representative cases of POLs in the skull and the mandible of a patient with MM stage III (Figure 1A-E). All patients with POLs in the mandible also had POLs in the skull. We evaluated the proportion of POLs found in the skull and the mandible based on the ISS. There were 37 patients in ISS stage I. Of them, eight (21.6%) had POLs in the skull, while two (5.4%) had POLs in the mandible. Out of the 43 patients in ISS stage II, 16 (37.2%) had POLs in the skull, while six (14.0%) had

POLs in the mandible. Out of the 18 patients in ISS stage III, 18 (100%) had POLs in the skull, while ten (55.6%) had POLs in the mandible. In POLs in both the skull and mandible, POL prevalence significantly increased as their ISS progressed ($p < 0.0001$).

Table 3 summarizes the proportion of POLs by sites of the mandible confirmed on CT and panoramic radiograph. POLs, confirmed by CT, occurred frequently from the mandibular ramus (n = 16; 88.9%) to the mandibular angle (n = 15; 83.3%) followed by the mandibular body (n = 12; 66.7%), the subcondylar process (n = 8; 44.4%), and the coronoid process (n = 2; 11.1%). There were no POLs confirmed in the symphysis. Four patients did not undergo panoramic radiographic examinations probably due to their low level of activity in daily life. POLs were confirmed in panoramic radiographs as follows: mandibular ramus (n = 12; 85.7%), mandibular angle (n = 11; 78.6%), mandibular body (n = 9; 64.3%), subcondylar process (n = 6; 40.0%), and coronoid process (n = 1; 6.7%), which almost had the same proportions as those confirmed by CT. Various POLs in panoramic radiographs and CT imaging of the mandible are available as supporting information (Supplementary Figure 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=45*).

Intraoral manifestations associated with POLs

Of the POL cases in the jawbone, only one (5.6%) had painless swelling with a smooth mucosal surface that coincided with the POL site without teeth. In this study, there were no patients with an abnormal perception of the trigeminal innervation area, pathologic fractures, or a poor quality of life due to POLs in the jawbone.

Comparison of bone mineral density between POLs and healthy sites

When comparing the bone mineral density between the affected and the healthy sites in the mandible in HU value, the POLs in the mandibular cortical bone (226-669 HU [503.2 mean ± 140.8 SD]) showed the same value as that in the mental foramen in several cases. However, it was statistically significantly lower than that of the healthy mandibular cortical bone (1236-1983 HU [1473.9 mean ± 167.7 SD]) and that of the mental foramen (289-998 HU [714.3 mean ± 188.6 SD]) ($p < 0.0001$).

This study investigated the prevalence of POLs in the mandible and their correlation with MM progress in patients with symptomatic MM. Our report was the first to show that POLs can occur in the mandible during the early stages of MM, especially in the mandibular ramus and at the mandibular angle. Furthermore, the expression proportion of POLs increased with MM stage progression, and panoramic radiographs proved useful in confirming MM-associated POLs.

The annual number of new MM cases in Japan was approximately six per 100,000 in 2018 (*17*). Although this proportion was nearly the same as those in the United States and Europe (*18,19*), it has remarkably increased year by year in Japan. In fact, the number of patients with MM in 2018 reached about eight times its number from the 1970s (*17*). MM is extremely rare in people under 30 years of age, with a reported frequency of 0.02% to 0.3%. Approximately 90% of cases occur in patients over 50 years (*2*). In our survey, 83 out of 98 (84.7%) were more than 50 years old, consistent with previous studies.

As mentioned earlier, MM can manifest as osteolytic lesions without subjective symptoms. Almost 80% of patients with MM have radiological findings on skeletal surveys most commonly affecting the following sites: vertebrae (65%), ribs (45%), skull (40%), shoulder (40%), pelvis (30%), and long bones (25%) (*20*). However, no studies examined the mandible, a site primarily evaluated by dental surgeons during DFI screening before chemotherapy (*10*). In our survey, the prevalence of POLs in the skull was 42.9%, similar to previous studies. As a new finding, POLs in the mandible were identified in 18.4% of the patients. Although POLs do not commonly occur in the mandible, we suggest that if osteolytic lesions unlikely to be associated with DFIs are found in the mandible of MM patients, the possibility of POLs should be considered.

As mentioned earlier, dental surgeons often evaluate the oral cavity and the jawbone as a pre-chemotherapy screening for DFIs in patients with hematologic malignancies, and if necessary, remove the foci during the extraction of the associated tooth (*10*). However, it should be noted that surgery on MM patients with POLs is prone to postoperative complications, reported to have occurred in as many as 20.8% of cases. These include abnormal bleeding, abnormal bone fractures, and SSI (*5*). In another study, the risk of developing

Table 3. Proportion of punched-out lesions by site of the mandible confirmed on CT and panoramic radiograph

Screening method	Sites of the mandible					
	Symphysis	Body	Angle	Ramus	Coronoid process	Subcondylar process
CT	0/18 (0%)	12/18 (66.7%)	15/18 (83.3%)	16/18 (88.9%)	2/18 (11.1%)	8/18 (44.4%)
Panoramic radiograph[†]	0/14 (0%)	9/14 (64.3%)	11/14 (78.6%)	12/14 (85.7%)	1/14 (6.7%)	6/14 (40.0%)

[†]Four patients did not undergo panoramic radiographic examinations probably due to their low level of activity in daily life.

bacterial infections such as septicemia and osteomyelitis in MM patients was seven-fold compared to the control subjects without previous hematologic malignancies. During the first year following diagnosis, the risk was 11-fold (*21*). In addition, a more progressed stage of ISS leads to easier infection by bloodstream pathogens and a higher mortality rate (*22,23*). Although there is still no valid literature reporting on the postoperative course for the oral maxillofacial region of MM patients with POLs, if surgery is required, we should carefully perform the differential diagnosis and explain to patients the benefits of surgery as well as possible complications.

Panoramic radiographs, a radiologic technique for producing a single image of the facial structures, including the dental arches and jawbones, are particularly good at visualizing the mandible with less three-dimensional bone overlap. On the other hand, panoramic radiographs have a three-dimensional curved zone, called the focal trough, in which anatomical structures are well defined (*24*). Objects outside the focal trough are blurred, magnified, reduced in size, and sometimes distorted to the extent of not being recognizable, which is more likely to occur at a site anterior to the mandible, including the anterior teeth and symphysis. These circumstances indicate that the diagnostic accuracy at sites outside the focal trough is relatively low (*24*). In this study, the number of POL cases in the mandible was as small as 18; thus, it is not definitive. However, the proportion of POLs in the mandibular body, mandibular ramus, and mandibular angle, which were relatively clear in panoramic radiographs, were overwhelmingly high. Furthermore, POLs were not found in the symphysis. Therefore, panoramic radiographs can be used for assessing the mandible of MM patients. In addition, the HU value in CT correlates with the degree of radiolucency in two-dimensional plain radiographs (*25*). Considering the results of our study, which showed that POLs had a similar or slightly lower bone mineral density than the mental foramen, comparison with the mental foramen can be a diagnostic reference when evaluating the mandible with panoramic radiography.

According to Cardoso *et al.*, the initial oral symptoms of MM that triggered consultation varied. Among these were painless gingival swelling, difficult swallowing, and paresthesia in the trigeminal distribution of division III (*26*). However, in this study, only one patient had oral symptoms consistent with the POL site presenting as painless swelling with a smooth mucosal surface.

This study has several limitations. First, this is a cross-sectional study; thus, the clinical course of POLs in the oral cavity has not been sufficiently examined. Second, oral symptoms associated with MM may appear over time. Therefore, further studies are required to investigate the clinical course of POLs in the mandible and the effects of dental and oral surgery on MM patients with concomitant POLs in the mandible. In addition, although the ISS is used for the staging of symptomatic MM in this study, Palumbo *et al.* proposed the Revised-International Staging System (R-ISS) in 2015, which combines the ISS with chromosomal abnormalities detected by interphase fluorescent in situ hybridization and serum lactate dehydrogenase level (*27*). R-ISS is expected to be a staging classification that better reflects the improved prognosis of patients after the approval of new drugs such as proteasome inhibitors (*e.g.*, carfilzomib) in 2016 and monoclonal antibodies (*e.g.*, daratumumab) in 2017 (*28,29*); further, it has also been applied to radiological diagnostic studies related to osteolytic bone lesions in recent years (*30*). In this study, this classification of MM may provide new insights into the impact of POLs in the jawbone on patient quality of life and of the hematologic treatment on POLs over time.

In conclusion, although the prevalence of POLs in the mandible is low, POLs in the mandible were confirmed in patients with symptomatic MM, and their prevalence increased as the MM stage progressed. Confirmation of POLs in the mandible is possible not only by CT but also by panoramic radiography, and the mental foramen is likely to be a reference for discrimination. Considering the reports that surgery on MM patients with POLs is prone to postoperative complications, dental surgeons need to differentiate POLs when examining DFIs in multiple myeloma patients before surgery.

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A low proportion of asymptomatic COVID-19 patients with the Delta variant infection by viral transmission through household contact at the time of confirmation in Ibaraki, Japan

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Abstract: We conducted a study to investigate the proportion of patients with asymptomatic coronavirus disease 2019 (COVID-19) infected with the Delta variant compared with those infected with the wild-type strain at the time of confirmation. A total of 504 patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by viral transmission through household contact in Ibaraki, Japan were included. The proportion of asymptomatic COVID-19 patients at the time of confirmation was compared between patients infected with L452R mutation strain from June to September 2021 and those infected with the wild-type strain from November 2020 to January 2021, and was found to be 14.2% and 28.8%, respectively (relative risk, 0.49; 95% confidence interval, 0.35-0.70). The proportion of asymptomatic COVID-19 patients by viral transmission through household contact was lower among the Delta variant than those among the wild-type strain at the time of confirmation. It might contribute to attenuation of transmission.

***Keywords*:** Delta variant, coronavirus disease 2019 (COVID-19), asymptomatic, Japan

Introduction

The Delta variant (also known as Pango B. 1.617.2 strain) is a lineage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was classified as a variant of concern (VOC) on May 11, 2021 (*1*). The estimated transmissibility of this variant is increased by 97% (*2*). VOCs bearing the L452R spike protein mutation demonstrated increased transmissibility, infectivity, and evasion of antibody neutralization (*3*). The Delta variant has been reported from 191 countries across all six World Health Organization regions and has become the dominant strain in many countries (*4*).

In Japan, as of November 2021, a surge of novel coronavirus disease 2019 (COVID-19) occurred five times, and a total of 1.7 million patients with COVID-19 were reported. The third wave with the wild-type strain peaked in January 2021, and the fourth wave with the Alpha variant dominance peaked in May 2021 (*5*).

Patients infected with the Delta variant *via* domestic transmission began to be confirmed in the latter half of May. The fifth wave of COVID-19, which was primarily caused by the Delta variant, occurred from the latter half of July 2021 to August 2021, with a daily reported number of patients ranging from 3,408 on July 15 to 25,858, the peak, on August 20. The proportion of SARS-CoV-2 virus strain with L452R mutation, which almost corresponded to the Delta variant in Japan, was 89% in the week from August 16 to August 22. However, the daily reported number of patients decreased rapidly after September, and was 17,702 on August 31, 1,568 on September 30, and 147 on October 25 (*6,7*). Although the development of vaccines and social interventions during July-August might have contributed to the decline in the number of patients, the cause of the rapid decline in the number of patients in the fifth wave in Japan has not been completely elucidated.

SARS-CoV-2 can be transmitted through contact with asymptomatic or pre-symptomatic individuals (*8*). A high proportion of asymptomatic patients may make the control of the COVID-19 outbreak difficult (*9*). However, the Delta variant may reduce the proportion of asymptomatic patients (*10,11*). One possible reason behind the rapid decline in the number of COVID-19 patients may be the decline in the proportion of asymptomatic or pre-symptomatic patients in the community, decreasing the undiscovered transmission sources. To the best of our knowledge, no reviewed study reported the proportion of asymptomatic COVID-19

patients among those infected with the Delta variant in Japan.

This study aimed to investigate the proportion of patients with asymptomatic COVID-19 infected with the Delta variant compared to those infected with the wild-type strain at the time of confirmation.

Study 1 on household transmission in southeastern Ibaraki

In this study, a cross-sectional study design was employed.

Study 1 was carried out in the southeastern area of Ibaraki, the jurisdiction of the Itako Public Health Center, and the Tsuchiura Public Health Center of the Ibaraki Prefectural Government in Japan. The area is located about 90 km east-northeast of Tokyo and has a population of 520,000.

In Ibaraki, no patients infected with a VOC were detected until February 2021. The first patient infected with N501Y mutation and L452R variant was detected in the twelfth week (March 22–28) and the twenty-fifth week (June 21–27), respectively. The proportion of patients infected with the L452R mutation strain was 53% in the week from July 19 to July 25, and 82% from August 9 to August 15 (*12*). The L452R mutation is also observed in other variants of interest, such as the Kappa variant. However, almost all patients infected with the L452R mutation strain in Japan were confirmed to be infected with the Delta variant on investigating RNA sequencing (*6,7*).

No patients were vaccinated against COVID-19 in Ibaraki until January 2021. The proportion of patients who were vaccinated twice was 85% for those aged ≥ 70 years, according to the data released on August 16. In contrast, it was < 20% for those aged < 60 years (*13*).

The eligible participants were patients with confirmed COVID-19, who were assumed to be infected through contact with another household patient with COVID-19 as defined by the Public Health Center. The procedure for participant involvement and data collection has been described in a previous study (*14*).

Participants during the wild-type strain dominant period included patients with confirmed COVID-19 between November 2020 and January 2021. Only a small number of patients had been reported during the first wave and the second wave, until October 2020, in the area. The number of patients increased during the third wave, from November 2020 to January 2021, in the area. B.1.1.214 strain was dominant among wild strains during the period in Japan (*15*). Patients infected with the Delta variant during June-September 2021, who had an L452R mutation detected in their specimen or the specimen of their contacts, were included. The first Delta variant was detected in June in Ibaraki (*12*). The Delta variant dominant fifth wave was observed from July to September though patients with Alpha variant constituted part of the patients at the beginning of the fifth wave (*7*).

In Japan, according to the Infectious Diseases Control Law (The Law), the public health center is notified of all COVID-19 cases (*16*). SARS-CoV-2 infections were confirmed using polymerase chain reaction (PCR) test with a cycle threshold value of 40, loop-mediated isothermal amplification test, antigen quantitative test, or monoclonal antigen qualitative test.

The public health center collected patient' data on demographics, symptoms, and history of vaccination based on this law.

We compared the proportion of asymptomatic patients by age group in the Delta variant dominant period with that in the wild-type strain dominant period. Relative risks were calculated using 95% confidence intervals (CI). In study 1, mean diagnostic delay for symptomatic patients was calculated for patients with the L452 mutation and with the wild-type strain. Statistical analyses were performed using R software, version 4.1-1 (R Foundation for Statistical Computing, Vienna, Austria).

The study protocol was approved on July 8, 2021, by the Ibaraki Prefecture Epidemiological Research Joint Ethics Review Committee (protocol number: R3-1). The study was implemented following the law and exempted from obtaining informed consent under "the ethical guidelines for life science and medical research on human subject" in Japan.

Study 2 on both household and non-household transmission in the entire Ibaraki

In study 2, we aimed to confirm findings in Study 1 to be applied in the entire Ibaraki as sensitive analyses, and to externally validate the results among non-household contacts.

In study 2, the entire Ibaraki prefecture, with a population of 2,840,000, was included. Patients with confirmed COVID-19 infection by known contact, both household and non-household, were included. We retrieved publicly available data disclosed on the official website of the Ibaraki prefectural government. The data included the date of onset of symptoms before disclosure but did not include information on L452R mutation detection. Participants during the wild-type strain dominant period included patients with confirmed COVID-19 between November 2020 and January 2021. Participants during the Delta variant dominant period included patients with confirmed COVID-19 in August 2021, regardless of the L452R mutation detection test result.

We compared the proportion of asymptomatic patients by age group in the Delta variant dominant period with that in the wild-type strain dominant period. Relative risks were calculated using 95% confidence intervals (CI).

Low proportion of asymptomatic COVID-19 patients among the Delta variant

In Study 1, the proportion of patients with asymptomatic COVID-19 infected *via* household transmission was 14.2% (41 out of 289) for patients with L452R mutation strain during June-September 2021 compared with 28.8% (62 out of 215) for patients with the wild-type strain during November 2020–January 2021 (relative risk, 0.49; 95% CI, 0.35-0.70). Among patients aged 20-59 years, the proportion of asymptomatic patients was 8.5% for patients infected with L452R mutation strain compared to 24.3% for patients with the wild-type strain (relative risk, 0.35; 95% CI, 0.18-0.66) (Table 1). Among unvaccinated patients, asymptomatic patients were 23 out of 102 (22.5%) aged 0-19 years, 7 out of 105 (6.7%) aged 20-59 years, and 4 out of 20 (20%) aged 60 years. Three out of 24 (12.5%) partially vaccinated patients were asymptomatic and 4 out of 28 (14.3%) completely vaccinated (≥ 2 weeks following the second vaccination) patients were asymptomatic.

Mean diagnostic delay was 2.57 days for infection with L452R mutation strain, and 3.61 days for patients with the wild-type strain.

In the entire Ibaraki in Study 2, the proportion of patients with asymptomatic COVID-19 infection by known contact was 13.7% during August 2021 compared to 30.3% during November 2020–January 2021 (relative risk, 0.45; 95% CI, 0.42-0.50). Among patients aged 20-59 years, the proportion of patients with asymptomatic COVID-19 was 10.6% in August 2021 compared to 28.1% during November 2020–January 2021 (relative risk, 0.38; 95% CI, 0.33-0.43) (Table 2). The proportion of patients with asymptomatic COVID-19 infected by unknown contact were 4.6% of 2,542 patients between November 2020 and January 2021 and 3.8% of 3,316 patients in August 2021.

Possible implications of findings

The proportion of patients with asymptomatic COVID-19 at the time of confirmation was lower among those infected with the Delta variant than those infected with the wild-type strain, both in household contacts, despite shorter diagnostic delay, in the southeastern part of Ibaraki (Study 1), and in contact with the whole Ibaraki (Study 2). The proportion was low, especially in the age group 20-59 years.

Several studies have reported a decline in the proportion of patients with asymptomatic COVID-19 and early onset of symptoms after exposure to the Delta variants (*9-11*). Our results are consistent with those in the literature.

Asymptomatic patients at the time of confirmation included both asymptomatic and pre-symptomatic patients. Symptomatic patients may be quarantined voluntarily or after confirmation of infection by visiting physicians, albeit asymptomatic or pre-symptomatic patients remain unaware of the infection and continue viral shedding in the community. Although pre-symptomatic patients later become symptomatic and may be isolated, most of the transmission to other contacts occurs either in the pre-symptomatic period or a few days after onset of symptoms (*11*). Therefore, a decrease

Table 1. The proportion of patients with asymptomatic COVID-19 at the time of confirmation infected *via* household transmission in the southeastern part of Ibaraki

Period	June–September 2021		November 2020–January 2021		Relative risk (95% confidence interval)
Mutation test	L452R mutation		No		
Age (years)	Patients *n*	Asymptomatic* *n* (%)	Patients *n*	Asymptomatic* *n* (%)	
0 - 19	103	23 (22.3)	45	12 (26.7)	0.84 (0.46-1.53)
20 - 59	142	12 (8.5)	103	25 (24.3)	0.35 (0.18-0.66)
60	44	6 (13.6)	67	25 (37.3)	0.37 (0.16-0.82)
Total	289	41 (14.2)	215	62 (28.8)	0.49 (0.35-0.70)

*Asymptomatic at the time of confirmation.

Table 2. The proportion of patients with asymptomatic COVID-19 infected by known contact in the whole of Ibaraki

Period	August 2021		November 2020–January 2021		Relative risk (95% confidence interval)
Age (years)	Patients *n*	Asymptomatic* *n* (%)	Patients *n*	Asymptomatic* *n* (%)	
0 - 19	1,452	253 (17.4)	416	139 (33.4)	0.52 (0.44-0.62)
20 - 59	3,099	327 (10.6)	1,522	427 (28.1)	0.38 (0.33-0.43)
20 - 39	1,806	189 (10.5)	758	220 (29.0)	0.36 (0.30-0.43)
40 - 59	1,293	138 (10.7)	764	207 (27.1)	0.39 (0.32-0.48)
60 -	496	111 (22.4)	604	204 (33.8)	0.66 (0.54-0.81)
60 - 79	403	85 (21.1)	422	136 (32.2)	0.65 (0.52-0.83)
80 -	93	26 (28.0)	182	68 (37.4)	0.75 (0.51-1.09)
Total	5,055	696 (13.7)	2,542	770 (30.3)	0.45 (0.42-0.50)

*Asymptomatic at the time of disclosure.

in the proportion of patients with asymptomatic or pre-symptomatic COVID-19 may contribute to a decrease in the number of infected patients in the next generation in the community (*9,17*).

The reason behind the rapid decrease in the number of patients with COVID-19 from September to October 2021 in Japan has not been sufficiently elucidated. In Ibaraki, since the Delta variant became predominant from mid-July, the number of patients with COVID-19 increased rapidly, resulting in the fifth wave. If this increase influenced symptomatic patients to quarantine themselves or visit physicians since August, the subsequent decrease in the proportion of unconscious or undiscovered sources of transmission combined with other factors, such as rapid development of vaccination in August-September 2021, might have contributed to the rapid attenuation of virus transmission.

Several months after vaccination, the preventive effect on infection may decrease among vaccinated persons, breakthrough infections may increase, and the proportion of patients with asymptomatic or pre-symptomatic COVID-19 may increase again (*10,18*). The number of infected patients with Delta variant increased again at the end of 2021 in Japan; it was replaced with Omicron variant in January, 2022. It is necessary to continue protective measures, such as wearing masks and ventilation and implementing booster vaccination.

This study had several limitations. First, this study employed a cross-sectional design; thus, the results did not show any causal relationships. Second, in Study 1, we defined patients with the earliest onset date as the index patients in a household without any patients with COVID-19 with apparent exposure to SARS-CoV-2. The index patients might have been misclassified as secondary patients. Third, the data in Study 2 were collected only through websites and their authenticity could not be confirmed.

Further studies on the Delta variant regarding its transmission dynamics and prediction using mathematical models are warranted.

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A review of four cases of COVID-19 medically evacuated by ambulance jet from Asian countries to Japan: Importance of strict infection control measures against multidrug-resistant organisms

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Abstract: International medical evacuation, which is an option to receive better medical care for travelers with emergencies staying in low- and middle-income countries, has been more challenging during the coronavirus disease 2019 (COVID-19) pandemic. We herein discuss our experience with four Japanese patients with COVID-19 who required medical evacuation from Asian countries during the pandemic. Of these, none of the patients had received a COVID-19 vaccine; three patients needed oxygen therapy on admission to our hospital; and one patient died due to respiratory failure on day 50 after hospitalization. It was observed that multidrug-resistant organisms were colonized in two patients after obtaining culture results based on active surveillance. Strict infection control measures against multidrug-resistant organisms should be implemented during the care of patients with COVID-19 who require medical evacuation from high-risk countries. Further, it is important to communicate timely updates regarding the patient's condition with travel assistance agencies as the patient's condition may rapidly change during the course of arranging the evacuation.

***Keywords*:** COVID-19, medical evacuation, multidrug-resistant organisms

An outbreak of coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China in December 2019, rapidly spread worldwide. The World Health Organization declared the COVID-19 outbreak as a pandemic on March 11, 2020 (*1*). As of December 12, 2021, a total of 268,934,575 COVID-19 cases, including 5,297,850 casualties have been reported across the globe (*2*). The pandemic has laid a heavy burden on medical facilities in many countries, and appropriate access to medical care has been often limited. Especially in low- and middle-income countries, receiving appropriate medical care has been difficult due to the lack of medical resources during the COVID-19 pandemic (*3*).

For overseas workers, medical evacuation is an option to receive better medical care in cases where appropriate medical care may not be available in their region of residence. For example, the evacuation of individuals infected with Ebola virus from West Africa to developed countries in Europe and the USA was associated with significantly improved mortality (*4*). However, international medical evacuation during the COVID-19 pandemic has been associated with more challenges because other countries, including the patient's home country, have also been affected by the pandemic, which continues to significantly restrict the availability of air ambulance flights, number of countries that accept these services, and availability of medical facilities that can receive these patients (*5*). Several studies reported collective medical evacuation including that of critical patients with COVID-19 conducted by army forces (*6-8*); however, few studies to date have provided detailed reports of the clinical characteristics of patients with COVID-19 medically evacuated from abroad. We herein describe the characteristics of Japanese patients with COVID-19 who were evacuated from abroad and discuss important lessons learned regarding infection control and arrangement for the medical evacuation of patients with COVID-19 during the pandemic.

Between January 2020 and October 2021, four hospitalized patients with COVID-19 required medical evacuation and were transferred to Japanese Red Cross Narita Hospital, a large tertiary teaching hospital with 714 beds located at a 20-minute drive from Narita International Airport in Chiba, Japan. Medical evacuation was arranged by the same medical travel assistance company for all the patients; the patients were transported by an air ambulance jet with the assistance of medical doctors and nurses. Clinical data of all the patients were retrospectively obtained from electronic medical records. Screening cultures for active

surveillance were performed according to the hospital protocol, which required evaluation of patients who were hospitalized abroad or who received invasive medical procedure abroad within the last three months. Samples were collected for cultures from stool, sputum, urine, and wounds, if available, using selective media. Vancomycin-resistant enterococci were screened using CHROMagar™ VRE medium (CHROMagar, Paris, France). Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and carbapenemase-producing *Enterobacteriaceae* were screened using CHROMagar™ ESBL agar (CHROMagar) and CHROMagar™ mSuper CARBAagar (CHROMagar). Carbapenemase genes were identified using the Xpert Carba-R cartridge and the GeneXpert system (Cepheid, CA, USA). Sputum, urine, and wound samples were also cultured using non-selective medium, and the identification and susceptibility of microorganisms were confirmed as usual. The study was approved by the Ethics Committee of the Japanese Red Cross Narita Hospital under the condition that the confidentiality of all personal data be maintained (approval no, JRCNH-749-01). The requirement for individual consent was waived given the retrospective, observational nature of the study.

Table 1 summarizes the characteristics of the patients. All the patients arrived in the hospital either late at night or early in the morning. The median patient age was 49.5 (range, 49-63), all patients were male and had been staying in the destination country for business purposes, and none of the patients had received a COVID-19 vaccine. Three of the four patients were infected in Indonesia, whereas the remaining patient was infected in Nepal. All patients were admitted to local hospitals. The median duration between symptomatic onset and local hospital admission was 3 (range 2-4) days. Three patients received high-dose oxygen therapy. The treatment for COVID-19 varied among the patients and included favipiravir and remdesivir in 3 and 1 patient, respectively. Antimicrobial therapy was provided to all patients. The median length of stay in the local hospital was 12.5 (range 4-15) days.

Three of the four patients needed oxygen therapy on admission to our hospital. Multidrug-resistant bacteria were present in the screening cultures of two patients. Carbapenem-resistant *Escherichia coli* was cultured from the stool and later confirmed as New Delhi metallo-beta-lactamase-producing *E. coli* in one patient. Additionally, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* were cultured from the sputum of the same patient. AmpC beta-lactamase overproducing *Enterobacter cloacae complex* was cultured from the stool in another patient. In patients with multidrug-resistant organisms, strict contact precautions were continued until discharge. Three patients recovered without sequelae. In the remaining patient, the respiratory condition worsened and was complicated with ventilator-associated pneumonia and COVID-19-associated pulmonary aspergillosis. Despite invasive ventilatory management and veno-venous extracorporeal membrane oxygenation, the patient died due to respiratory failure on hospital day 50.

As reflected in these four cases, strict infection control measures for multidrug-resistant organisms should be implemented during the care of patients who require medical evacuation from high-risk countries. Travel to South or Southeast Asia and history of medical practices (*e.g.*, hospitalization, antibiotic administration, invasive treatment including surgery, device placement) at the destination country are considered as major risk factors for colonization of multidrug-resistant organisms (*9,10*). Additionally, 10% of patients who were hospitalized abroad and exhibited multidrug-resistant bacteria were reported to subsequently develop symptomatic multidrug-resistant infections (*9*) and an outbreak of multidrug-resistant organisms originating from a traveler who was previously hospitalized abroad was reported in a Japanese hospital (*11*). All four patients reported herein were hospitalized in the destination country before evacuation and received antimicrobial treatment. We implemented strict contact precautions, performed active surveillance according to the institutional protocol, and determined that two patients were colonized with multidrug-resistant organisms. Transmission to other patients in the COVID-19 ward was not observed. Our experience suggests that strict infection control including contact isolation and active surveillance should be considered during planning for the admission of patients who require medical evacuation from abroad.

Vaccination for COVID-19 is important even for international travelers. Vaccination has been proven to significantly reduce the rate of infection and the severity of COVID-19 (*12,13*). None of the four patients in the current report were vaccinated against COVID-19. The Centers for Disease Control and Prevention recommends that all international travelers complete the COVID-19 vaccine series prior to travel (*14*). Vaccination against COVID-19 is necessary for international travelers because adequate medical care might be inaccessible during the COVID-19 pandemic.

Close communication to share updated information about the clinical condition of patients with the medical travel assistance company is key for successful medical evacuation. The patient's condition may rapidly change during the arrangement for evacuation. In fact, the respiratory status in two of the four patients significantly changed before transportation to our hospital. Hypoxia worsened in one patient and improved in another patient after the first contact between the medical travel assistance company and our hospital for the arrangement of evacuation.

We also faced an ethical dilemma in terms of bed capacity. During the surge in the number of local COVID-19 cases, our hospital was nearly full or

Table 1. Clinical details of four patients with coronavirus disease 2019 who required medical evacuation

Items	Case 1	Case 2	Case 3	Case 4
Date of evacuation	December 2020	June 2021	July 2021	July 2021
Duration between initial contact and evacuation (days)	5	5	2	2
Time of admission	8:35	22:07	21:24	20:37
Patient demographics and background				
Age (year), sex	49, male	63, male	50, male	49, male
Comorbidities	Diabetes mellitus	Hypertension	Abdominal aortic aneurysm	Hypertension Diabetes mellitus
COVID-19 vaccination history	None	None	None	None
Purpose of international travel	Business	Business	Business	Business
Country	Indonesia	Nepal	Indonesia	Indonesia
Duration of stay in the destination country	3 months	6 months	Unknown	Unknown
Clinical condition and treatment before evacuation				
Duration from the onset of symptoms and admission to local hospital (days)	3	2	3	4
Oxygen therapy	High-flow nasal cannula	Oxygen mask (max 15 L/min)	None	Oxygen mask (max 6 L/min)
Treatment for COVID-19	Favipiravir Remdesivir Methylpredonisolone Enoxaparin Tocilizumab	Dexamethasone Methylpredonisolone Enoxaparin Ivermectin	Favipiravir (discontinued for two days due to drug shortage)	Favipiravir Dexamethasone Heparin
Antimicrobial use	Azithromycin	Ceftriaxone Meropenem	Ceftriaxone	Cefoperazone/sulbactam Levofloxacin
Length of hospital stay in local hospital (days)	13	15	4	12
Clinical condition and treatment after evacuation				
Respiratory status on admission	SpO_2, 97% at 3L/min O_2	SpO_2, 90% at 15L/min O_2	SpO_2, 92% at room air	SpO_2, 97% at 6 L/min O_2
Culture results based on active surveillance to detect multi-drug resistant organisms	No specific organism in sputum, stool, and urine	*Escherichia coli* (NDM-CPE) from stool *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* from sputum No specific organism in urine	*Enterobacter cloacae* (AmpC beta-lactamase overproducing) in stool No specific organism detected in urine and sputum	No specific organism in stool and urine
Oxygen therapy	Nasal canula (max 3L/min)	Veno-venous ECMO	None	Oxygen mask (6 L/min)
Treatment for COVID-19	Dexamethasone Heparin	Baricitinib Methylpredonisolone	None	None
Major complications	None	CAPA, VAP due to *S. maltophilia*, CRBSI due to *E. coli* (ESBL)	None	None
Length of hospital stay (day)	6	49	7	6
Outcome	Survived	Died	Survived	Survived

CAPA, coronavirus disease 2019-associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; CRBSI, catheter-related blood stream infection; ECMO, extracorporeal membrane oxygenation; ESBL, extended-spectrum beta -lactamase; NDM-CRE, New Delhi metallo-beta-lactamase-producing carbapenem-resistant *Enterobacteriaceae*; VAP, ventilator-associated pneumonia.

overcrowded. Providing a bed to a patient requiring medical evacuation would prevent the admission of a local patient with COVID-19. Thus, we prioritized the patients who resided in or around Chiba. In all four cases, the medical travel assistance company directly contacted the hospital to determine the availability of a space for the patient. In ideal circumstances, a comprehensive bed control system is expected to provide beds both for local patients and those who require medical evacuation from abroad.

In conclusion, our experience with four patients with COVID-19 who required medical evacuation from Asian countries during the pandemic illustrates the need for implementation of strict infection control measures against multidrug-resistant organisms. Further, it is important to communicate timely updates regarding the patient's condition with travel assistance agencies during the arrangement of medical evacuation.

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LETTER

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Perspectives on countermeasures against COVID-19 in the remote islands of Yaeyama region, Okinawa, Japan

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Abstract: Numerous difficulties unique to remote island regions exist in the fight against coronavirus disease 2019 (COVID-19). For example, in the Yaeyama Medical Region (Okinawa, Japan), there are only clinics without beds on constituent islands. As medical resources are limited on remote islands, a single outbreak can put the entire medical system at risk. In addition, local governments need to maintain economic support while taking measures to contain outbreaks. For future COVID-19 countermeasures, it is essential to establish a response team in the regional hospital to conduct on-site epidemiological surveys as early as possible in a pandemic. In addition, distributing effective oral antivirals to remote islands may reduce the spread of infection and the number of severe cases requiring off-region transfer.

***Keywords*:** epidemiological surveys, off-region transfer, infection control, oral antivirals

Okinawa Prefecture is located in southwestern Japan and comprises 160 islands (*1*). The most southwestern part of Okinawa is the Yaeyama Medical Region, with a population of approximately 50,000. The regional hospital (Okinawa Prefectural Yaeyama Hospital) located on Ishigaki Island, the main island, plays a pivotal role in the medical system of the region. It is surrounded by small- and medium-sized outlying islands (Iriomote, Kohama, Hateruma, Taketomi, Yonaguni, and Kuroshima), where clinics without beds are the only medical facilities, and barely inhabited remote islands (Hatoma and Aragusuku) without clinics. For simplicity, small- and medium-sized outlying islands without inpatient beds are referred to as "remote islands". Each clinic in the Yaeyama region is staffed by only one doctor and nurse, with no inpatient facilities. Patients who require advanced medical care are transferred to the regional hospital in Ishigaki Island or the larger hospitals in mainland Okinawa only when the weather and the situation permit. The Japan Coast Guard and Ground Self-Defense Force are primarily responsible for transfers. However, clinics provide adequate non-critical health care because the staff are familiar with inhabitants' health status and social backgrounds.

The Yaeyama Medical Region has experienced numerous outbreaks since its first coronavirus disease 2019 (COVID-19) case in April 2020. By January 2022, three large outbreaks that required external assistance occurred in the Yaeyama region. One of them occurred in a nursing home on the remote Yonaguni Island (*2*), and the others occurred on Ishigaki Island. Assistance received included medical resources and staff from the Okinawa Prefectural Headquarters for COVID-19 (the Headquarters), the Disaster Medical Assistant Team (DMAT; a Japanese governmental medical aid team dispatched in disasters) (*3*), and Japan Heart (a nonprofit organization) (*4*). The head of the chain of command for COVID-19 measures is the prefectural governor, under whom the Headquarters has been established. COVID-19 countermeasures on remote islands involve a variety of region-specific difficulties:

i) Limited medical resources because of geographical factors When a COVID-19 outbreak occurs on remote islands, interventions such as epidemiological surveys and treatment of patients with severe disease can be conducted with support from the regional hospital. When large outbreaks occur, especially in nursing facilities on remote islands, assistance from outside the region is often required. In such situations, only minimal on-site treatment such as oxygen supply from temporary oxygen tanks, oral dexamethasone, and intravenous neutralizing antibodies can be provided.

Moreover, although the regional hospital has an intensive care unit with several beds, it does not have advanced medical equipment such as extracorporeal membrane oxygenation. In a large outbreak in a nursing facility in Yonaguni Island, more than 30 facilities

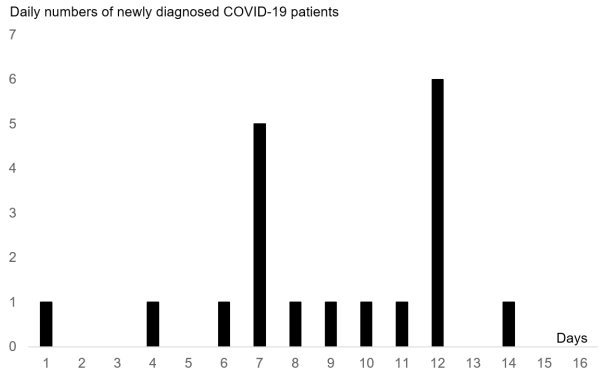

Figure 1. Residents who tested positive by nasal pharyngeal swab severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) PCR test in the primary cluster in Iriomote Island, the largest remote island in the Yaeyama region, in July 2020. Eighteen residents were diagnosed with COVID-19, and none developed severe disease requiring oxygen supply. The vertical axis displays the number of patients with disease onset occurring each day. On the horizontal axis, "days" shows the number of days between "day 1" to the day of disease onset for each patient. "Day 1" is when the first COVID-19 patient was diagnosed on Iriomote Island.

residents were infected (*2*). Transferring these patients to the main island was almost unfeasible, and they were treated with steroids and neutralizing antibodies on site.

ii) Closer household ties Remote island residents generally have closer household ties than urban residents. This can be a drawback in preventing the spread of infection and protecting the privacy of those affected.

iii) Downside effect on the economy Almost all remote islands depend on tourism for financial support. However, measures to prevent infection, such as shortening operating hours or banning alcohol, often conflict with promoting economic activities.

The solutions currently in place include the following:

i) Early implementation of an epidemiological survey In the Yaeyama region, the first COVID-19 cluster was successfully suppressed in western Iriomote Island in July 2020, before COVID-19 vaccines were available. Medical staff from the regional hospital were dispatched twice to conduct real-time polymerase chain reaction (RT-PCR) testing of nasal pharyngeal swabs to detect Severe Acute Respiratory Syndrome Coronavirus 2. Among 69 residents who had contact with COVID-19 patients, 18 tested positive (Figure 1), but no severe cases were reported. This experience suggests that early implementation of on-site epidemiological surveys and quarantine may reduce the impact ("COVID-19 Countermeasures in Small Remote Islands - An On-Site Study on Cluster Response that Occurred in the Western District of Iriomote Island" from the first author's presentation at the Joint Conference on Global Health 2020, Tokyo, Japan).

ii) Active promotion of infection prevention and vaccination Hospitals, clinics, and local governments in the Yaeyama region have raised residents' awareness of COVID-19. Grassroots campaigns have been effective because of the small population. By March 2022, more than 95% of residents aged over 65 years in the Yaeyama region had received at least one dose of vaccine.Moreover, in Ishigaki City, 82.5% of residents aged > 65 years had received three doses by March 14, 2022. This coverage far exceeds the national (69.9% on March 14, 2022) and prefectural (approximately 60% on March 7, 2022) averages in the same week (*5*).

Vaccination is crucial to reduce the number of off-island patient transportation and reliance on outside assistance. In addition, minimizing the number of residents with COVID-19 is beneficial to the region's economy.

iii) Active promotion of antigen testing and oral antivirals Although the Yaeyama region has some experience in controlling COVID-19 outbreaks on remote islands, establishing a fixed emergency response team and scheme to dispatch medical staff from the main island is ongoing. In addition, we suggest lowering the antigen testing threshold (using PCR, if available) on remote islands. Without this, future larger outbreaks may be challenging to manage and cause substantial damage.

We also propose to expand treatment options at remote island clinics. For example, oral antivirals are more straightforward to administer than intravenous agents, as there is no space for infectious patients in small clinics. Furthermore, oral antivirals could reduce the risk of severe disease and the need for off-region transfer.

As of March 2022, no COVID-19-specific medications have been provided to remote islands in the Yaeyama region beyond Ishigaki Island. We suggest that government, local authorities, and pharmaceutical companies prioritize remote islands to distribute the latest drugs.

In conclusion, delivering quality and quantity of health care on remote islands poses many challenges. There is an urgent need to establish specific countermeasures, considering the region-specific background and the latest evidence.

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Conflict of Interest: The first author (K.K.) is a medical counselor for Ishigaki City and received a daily allowance for three days in 2021. The other authors have no conflicts of interest to disclose.

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