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Normal daily life in Japan with relaxation of COVID-19-related border measures
– Shibuya Scramble Crossing –

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COVER PHOTO OF THIS ISSUE

Normal daily life in Japan with relaxation of COVID-19-related border measures – Shibuya Scramble Crossing. Starting October 11, 2022, the border control measures for entry into Japan have been updated, and regulations regarding COVID-19 testing and quarantine after entry, as well as entry restrictions for foreign nationals have been relaxed. Many social events have returned to normal, including the return of large crowds of Halloween partygoers at Shibuya Scramble Crossing.

(Photo by *Riri Saito*)

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Implementation of two novel schemes for patients on dialysis as a response to the COVID-19 surge in Tokyo

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Abstract: The Japanese government recommended hospitalization of patients on dialysis once they tested positive because of their high COVID-19 mortality rate and definite need for periodic dialysis. However, after experiencing the Delta variant surge, strategic changes towards outpatient care for mild or asymptomatic cases, along with strengthening emergency preparedness were needed. Facing the Omicron surge, the Tokyo Metropolitan Government introduced two novel schemes: *i*) a temporary medical facility with a dialysis center for infected patients on hemodialysis, which started admitting patients on dialysis on January 20, 2022, to provide additional bed capacity and access to hemodialysis and *ii*) a transportation scheme for patients who need travel to maintenance dialysis facilities from their homes, which was introduced on February 5. The Tokyo Metropolitan Government, cooperating with some nephrology experts, announced these schemes and urged local dialysis facilities to change strategies, providing information regarding infection prevention measures and treatments in online seminars on February 3 and 7. Consequently, promoting outpatient care did not lead to an increase in the case fatality ratio (CFR) in patients on dialysis with COVID-19 in Tokyo during the first Omicron surge (January 7 to February 10, 8.2%; February 11 to March 31, 5.5%). Furthermore, after an additional online seminar on July 20, the CFR dramatically declined in the second Omicron surge (July 8 to September 8, 1.2%). Implementation of public health intervention and careful communication with local dialysis facilities were both crucial to the strategic changes. To maintain essential health services, emergency preparedness should be cultivated during regular times.

***Keywords*:** policy, maintaining essential health services, emergency preparedness

Introduction

Patients receiving dialysis have an increased risk for severity of COVID-19 and a higher mortality rate than the general population (*1*). Considering the enhanced vulnerability of patients receiving dialysis to COVID-19 and their need for periodic hemodialysis, the Japanese government policy recommends that patients receiving dialysis with COVID-19 be hospitalized, even if they have only mild symptoms or are asymptomatic. However, when newly diagnosed cases were drastically increasing, hospitalization of each infected dialysis patient was, despite the governmental policy, unfeasible owing to hospital overload.

The surge in Delta variant infection struck Tokyo in the summer of 2021, and hospitals were overcrowded with moderate to severe cases. The COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, Japanese Society for Dialysis Therapy, and Japanese Society of Nephrology reported that it was "nearly impossible" to find a transfer destination even if an inpatient's condition worsened (*2*).

Emergency preparedness in dialysis facilities before the Omicron era

Having experienced recurrent shortages of hospital beds, however, not a small number of dialysis facilities were still unwilling to perform dialysis for patients with asymptomatic or mild COVID-19. It can be assumed that, for one thing, this was due to the potential risks of nosocomial infection. Concerning infection control measures, the Japanese Association of Dialysis Physicians published guidelines for preventing infection in maintenance hemodialysis facilities (*3*). However, according to a national questionnaire survey, from October to November 2020, some dialysis facilities performed inadequate infection control measures, including personal protective equipment use (especially face shields or eye guards), bed spacing, and exchanging bed linens (*4*).

In such a situation, the Task Force Committee, taking the leadership, had been releasing requests to physicians working at dialysis facilities for flexibly dealing with fluid COVID-19 situations and advocating for several

strategies regarding preparedness and responses to such public health emergencies (*2,5,6*). These strategies included cooperative work with authorities such as prefectural governments, efficient triage and effective use of hospital beds, patient education, promoting vaccination, proactive use of neutralizing antibody treatments, and implementation of infection control measures at each dialysis facility. In line with those strategies, after the Delta wave, we, the public health officials of the Tokyo Metropolitan Government, cooperating with nephrology experts including the chairperson of the Task Force Committee, reviewed the medical provision system and attempted to make improvements by, for instance, hosting online discussion seminars with local dialysis hospitals and asking to increase bed capacity in preparation for probable upcoming larger waves of infection.

Nevertheless, in January 2022 with the advent of the Omicron variant, an acceleratingly increasing number of new positive cases in Tokyo immediately threatened the local medical provision system and patients needing dialysis.

Two novel schemes aiming to change the strategy of outpatient dialysis in response to the Omicron BA.1 surge

In response to the first Omicron surge, the Tokyo Metropolitan Government set up two novel schemes: *i*) a temporary medical facility with a dialysis center for infected patients who needed hemodialysis and *ii*) a transportation scheme utilizing specialized negative pressure vehicles for outpatients needing transport from home to their maintenance dialysis facilities (Figure 1). The temporary medical facility could offer additional local bed capacity for patients needing dialysis. In particular, the hospital bed turnover rate could be improved by accommodating already hospitalized patients who still need isolation despite their symptoms being relieved (Figure 1A). Thus, the temporary medical facility enabled more efficient and effective use of medical resources. The transportation scheme provided access to maintenance dialysis facilities for patients with COVID-19 who could not use public transportation, as mentioned in the World Health Organization guidance for maintaining essential health services (*7*). Apart from these newly introduced schemes, the Tokyo Metropolitan Government had established another scheme to provide neutralizing antibody treatment for indicated outpatients with COVID-19 by transporting them to existing temporary medical facilities (without dialysis functions) (*8*). This scheme could also be adapted for patients on dialysis (Figure 1B). As a whole, clarifying the division of roles and responsibilities for local stakeholders (authorities, hospitals, and clinics), these schemes made strategic changes, from hospitalization of all positive patients needing dialysis to outpatient care if the patients were asymptomatic or had mild COVID-19 symptoms. In doing so, hospital beds could be allocated for patients with more severe conditions.

Implementation of the temporary medical facility with the dialysis center and its functions

The temporary medical facility, with the dialysis center, which had a maximum capacity of 150 beds exclusively

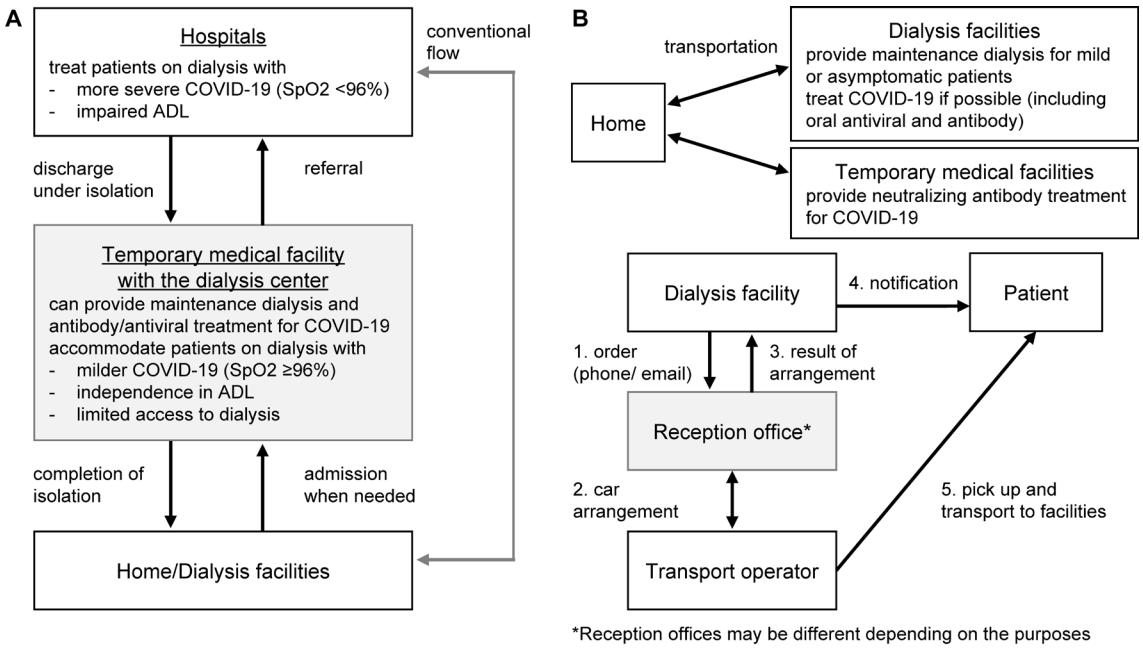

Figure 1. Schematic images of the temporary medical facility with the dialysis center (A) and the transportation scheme for patients on dialysis (B). Figure 1A illustrates how the temporary medical facility with the dialysis center could provide an additional capacity of beds between hospitals and homes. Figure 1B shows the scheme of transportation of patients needing dialysis from their homes to maintenance dialysis facilities (mainly clinics) or other temporary medical facilities.

for patients with COVID-19, was established on December 28, 2021, by repurposing an old building that used to be a private dialysis hospital (*9*). At first, only non-dialysis patients were admitted to the facility, and it started to admit patients receiving dialysis on January 20, 2022. The dialysis center was installed within the facility, where 10 dialysis machines and the same number of exclusive beds were prepared. Therefore, if two cycles of dialysis were performed for each bed, up to 20 patients could receive dialysis daily. Dialysis could be performed four days a week. Doctors (at least one nephrologist when dialysis was performed), clinical engineers, nurses (especially those who had been unemployed to not put a burden on hospitals), nurse assistants, and administrative officers worked at the facility. Some over-the-counter medicines, prescribed medicines for symptomatic treatment, and medication for performing dialysis and oxygen (only used in an emergency for patients on dialysis) were available. Treatments with neutralizing antibodies and oral antivirals for COVID-19 (sotrovimab and molnupiravir) could also be performed for indicated patients. Only minimum necessary clinical testing was available, such as blood gas analysis. The facility was not equipped for chest radiography. Therefore, the temporary medical facility with the dialysis center was fundamentally no more than a temporary accommodation where dialysis and isolation were possible. Given that patients receiving dialysis have a higher risk of severe COVID-19, those showing deterioration (such as oxygen saturation < 96%) are not basically admitted and should be immediately transferred to the hospital. To secure a hospital referral, several local hospitals, including university hospitals, were designated as backup hospitals. However, when hospitals were particularly overcrowded, patients on dialysis who were in relatively severe condition could only be admitted to the temporary medical facility for a short time until an appropriate hospital was found.

The schematic of the temporary medical facility with the dialysis center is shown in Figure 1A. The facility could accommodate the following patients: those already hospitalized who still required isolation despite their symptoms being resolved, patients isolated at home who had difficulty receiving maintenance dialysis at their regular dialysis facilities, and patients receiving dialysis who called an ambulance for COVID-19 symptoms but could not find a transfer destination. In addition, patients seeking antibody treatment could also be admitted to other temporary medical facilities in the same way. When admitting and discharging patients receiving dialysis, it was crucial to cooperate with the patients' maintenance dialysis facilities or hospitals in case they were being hospitalized. Accordingly, patient information could be shared regarding the dialysis conditions, clinical course of COVID-19, and schedule for returning to regular dialysis at maintenance dialysis facilities after completing isolation.

We hosted an online seminar on February 3, 2022, inviting all dialysis hospitals in Tokyo. The seminar announced the newly established temporary medical facility with the dialysis center. Hospitals were requested to consider transferring their inpatients who still required days of isolation despite their symptoms being already resolved. In total, 94 of 172 dialysis hospitals (54.7%) attended the seminar.

Implementation of the transportation scheme and announcement of the strategic changes for dialysis facilities

Figure 1B shows the overview of the transportation scheme. This transportation system, introduced on February 5, 2022, enabled each dialysis clinic to order specialized negative pressure vehicles for its patients, encouraging it to perform outpatient dialysis for those with mild or asymptomatic COVID-19. Furthermore, patients with mild COVID-19 symptoms who need dialysis could be transferred to temporary medical facilities (either the one with the dialysis center or others) to receive sotrovimab. This strategy could expectedly reduce the risk of the condition worsening, at least for those infected with the Omicron BA.1 subvariant (*10,11*); in addition, it could not only ensure the facilitation of outpatient dialysis but also alleviate the burden on the whole medical provision system.

We hosted another online seminar on February 7, 2022. We invited almost all dialysis facilities in Tokyo, including clinics, to announce these schemes and to call on the strategic changes, emphasizing the importance of the division of roles and responsibilities for all. Among 442 dialysis facilities in Tokyo, 258 (there could be double-counts) attended the seminar. At the workshop, we encouraged dialysis facilities to prescribe oral antivirals (molnupiravir) upon diagnosis of COVID-19 if indicated. Furthermore, some lectures were provided based on the guidelines (*3*) to prevent nosocomial infection among patients with COVID-19 during dialysis at such facilities. After that seminar, the Tokyo Metropolitan Government began the subsidy program that covered the cost of infection prevention, such as personal protective equipment, as financial incentives for maintenance dialysis facilities performing outpatient dialysis for patients who tested positive for COVID-19.

Facing the second Omicron surge that began in early July, we hosted a similar online seminar on July 20 again. Of 447 dialysis hospitals and clinics, 233 (52.1%) attended this seminar.

Effects of these schemes and the strategic changes on the case fatality ratio (CFR) in patients on dialysis during the Omicron BA.1/2 and BA.5 surges

Figure 2 shows the weekly new positive cases and deaths

in patients on dialysis from January to early September 2022 in Tokyo. The registry data of national patients needing dialysis with COVID-19, publicly released by the Task Force Committee, were collected from the websites of the Japanese Association of Dialysis Physicians and another related organization (*12*). There were two waves of infection during that period (so-called "sixth and seventh wave"), which were caused mainly by the Omicron BA.1/BA.2 and BA.5 subvariants, respectively. Notably, there was a dramatic decrease in the number of reported deaths in the seventh wave.

To calculate the CFR, we separated the study period into four different periods: period 1, before the strategic changes, from January 7 to February 10; period 2, the rest of the sixth wave, after the strategic changes, from February 11 to March 31; period 3, between the waves, from April 1 to July 7; period 4, during the seventh wave, from July 8 to September 8 (Figure 2). Since the calculation of the CFR from the registry data was a real-time estimation, the CFR could be underestimated when cases were increasing owing to the time delay from onset to death (*13*). To mitigate the bias, we exploited an alternate formula for the CFR, where the number of reported deaths was divided by the sum of the number of reported deaths and cases recovered from the disease (*14*).

The reported number of deaths and recovery over those periods was respectively as follows: period 1, seven and 78; period 2, 18 and 308; period 3, four and 150; period 4, five and 426. The CFRs during periods 1–4 were 8.2%, 5.5%, 2.6% and 1.2%, respectively. Using R software version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) (*15*), we conducted Fisher's exact test with the number of reported deaths and recovery to compare period 1 and other periods. Two-sided p-values were 0.32 for period 1 *vs.* period 2, 0.057 for period 1 *vs.* period 3 and 0.0010 for period 1 *vs.* period 4. Even though there was a matter of multiple comparisons, the p-value of period 1 *vs.* period 4 could be interpreted as statistically significant. Note that these figures could be biased owing to the reported time delay; for instance, if it takes longer to report patients' recovery than their death from the time of diagnosis, the CFR of period 1 can be overestimated. Additionally, we could not rule out the possibility that more death cases had been unreported during period 4 than during periods 1 and 2.

Having said that, there seemed to be a striking difference in CFR between these two waves. The number of hospital beds for patients receiving dialysis was not increased so much during those periods. One possible explanation could be that our public health measures were fairly effective, although it took a few months to fully produce the effect because the strategic changes required several processes in each dialysis facility including making procedure documents, procuring equipment, education and registering for prescription antivirals. The mechanism of how promoting outpatient dialysis can improve CFR in COVID-19 patients can be considered to be, for one thing, associated with improved accessibility to dialysis, which contributed to minimizing the disruption of dialysis schedules of patients. Skipping

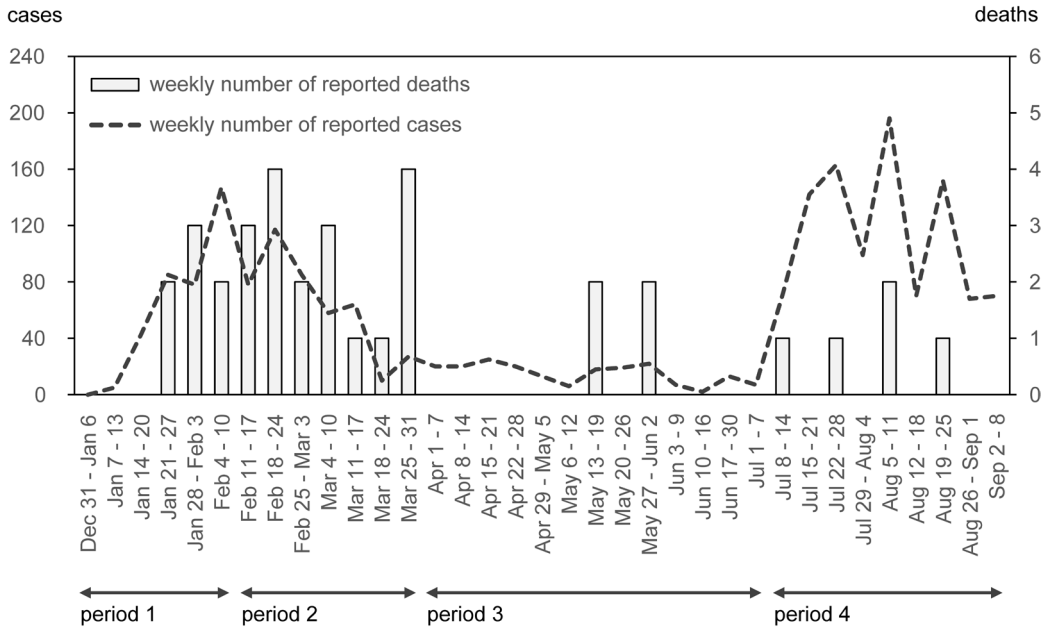

Figure 2. Weekly new positive cases and deaths in patients on dialysis from January to early September 2022 **in Tokyo.** The weekly number of reported deaths (bar) and new positive cases (dotted line) is shown from the beginning of the first Omicron surge to the second surge. The temporary medical facility with the dialysis center started admitting patients on dialysis on January 20, 2022 and the transportation scheme started on February 5, and they were subsequently announced on February 3 and 7. Four periods for calculating the case fatality ratio are indicated. Data were derived from weekly cumulative data released by the Task Force Committee. The number of weekly new positives (deaths) was calculated by comparing the cumulative numbers of positives (deaths) in consecutive weeks.

regular hemodialysis and not receiving dialysis for three days or more can impose excessive risk on patients, probably leading to deterioration in COVID-19 patients. Another explanation for reduced CFR may involve vaccination status. Unfortunately, data on COVID-19 vaccination coverage, specifically in patients on dialysis, were not available. Yet we instead collected data on vaccine coverage among people aged ≥ 65 years in Tokyo (*16*). At the beginning of period 1 (January 7), only 0.2% of people aged ≥ 65 years had received third shots. On February 25 (nearly in the middle of the sixth wave), the coverage ratio reached 50%. Regarding the coverage ratio of the fourth dose in the same population, 10.1% had received fourth shots at the beginning of period 4 (July 8). As early as August 8, the figure exceeded 50%, although this just coincided with the peak of the surge of infection. Therefore, the size of the immunized population might be smaller during periods 1 and 2 than during period 4; this factor could contribute to the improved CFR in period 4 to a certain degree. Other possible factors, which could affect CFRs include differences in herd immunity and viral pathogenicity between these two waves. Since available data and evidence are currently limited, future studies are needed to discuss these factors.

Conclusions

In this study, we observed a dramatic decrease in CFR in patients on dialysis during the seventh wave of COVID-19. Although the major contributing factor to this change has not been defined and needs further investigations, we believe, at least in part, our public health measures had an important role. Through our practices, we reconfirmed the importance of not only supplying necessary resources but also careful communication with local dialysis facilities. In particular, describing the situations with data, the definite need for the strategic changes and appropriate infection prevention measures were all important to collectively respond to the crisis.

Providing appropriate medical care for patients receiving dialysis with COVID-19 amid the surge of infection has been a formidable challenge. Not only does hospitalization become more challenging, but dialysis access can be seriously limited. To sustain the local medical provision system for them, effective hospital bed use, maintaining dialysis sessions and proactive treatments such as oral antivirals and neutralizing antibodies for indicated patients are of paramount importance. For that purpose, the combined strategies of improving the dialysis provision system and reducing demands, including efforts to prevent the spread of infection at each facility during regular times, are needed. Such emergency preparedness for maintaining essential health services, namely maintenance dialysis, should be cultivated to respond better to emergencies.

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

References

1. Terada M, Ohtsu H, Saito S, Hayakawa K, Tsuzuki S, Asai Y, Matsunaga N, Kutsuna S, Sugiura W, Ohmagari N. Risk factors for severity on admission and the disease progression during hospitalisation in a large cohort of patients with COVID-19 in Japan. BMJ Open. 2021; 11:e047007.
2. Kikuchi K, Yamakawa T, Ryuzaki M, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, the Japanese Society for Dialysis Therapy, and the Japanese Society of Nephrology. The notification about the current situation of hospitalization arrangement for dialysis patients infected with COVID-19 and requests to dialysis facilities. *http://www.touseki-ikai.or.jp/htm/03_info/doc/20210802_current_status_of_hospitalization_adjustment.pdf* (accessed September 15, 2022). (in Japanese)
3. The Japanese Association of Dialysis Physicians. Guidelines for Standard Hemodialysis Procedure and Prevention of Infection in Maintenance Hemodialysis Facilities (5th edition). *http://www.touseki-ikai.or.jp/htm/05_publish/doc_m_and_g/20200430_infection%20control_guideline.pdf* (accessed September 15, 2022). (in Japanese)
4. Sugawara Y, Iwagami M, Kikuchi K, Yoshida Y, Ando R, Shinoda T, Ryuzaki M, Nakamoto H, Sakai K, Hanafusa N, Kashihara N, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, the Japanese Society for Dialysis Therapy, and the Japanese Society of Nephrology. Infection prevention measures for patients undergoing hemodialysis during the COVID-19 pandemic in Japan: a nationwide questionnaire survey. Ren Replace Ther. 2021; 7:27.
5. Kikuchi K, Yamakawa T, Ryuzaki M, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, the Japanese Society for Dialysis Therapy, and the Japanese Society of Nephrology. Recommendations for ensuring medical care for dialysis patients with COVID-19 in Japan. *http://www.touseki-ikai.or.jp/htm/03_info/doc/20210120_dialysis_medical_care_2.pdf* (accessed September 15, 2022). (in Japanese)
6. Kikuchi K, Yamakawa T, Ryuzaki M, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, the Japanese Society for Dialysis Therapy, and the Japanese Society of Nephrology. The notification about use of antibody cocktail therapy for COVID-19 at clinics without beds. *http://www.touseki-ikai.or.jp/htm/03_info/doc/20211001_0_use_of_antibody_cocktail_therapy.pdf* (accessed September 15, 2022). (in Japanese)
7. World Health Organization. Maintaining essential health services: operational guidance for the COVID-19 context, interim guidance, June 1 2020. *https://www.who.int/publications/i/item/WHO-2019-nCoV-essential_health_services-2020.2* (accessed September 15, 2022).
8. Ohmagari N. How did the Tokyo Metropolitan Government respond to COVID-19? Glob Heal Med. 2022; 4:67-70.

9. Tokyo Metropolitan government. The 2746th press release. *https://www.metro.tokyo.lg.jp/tosei/hodohappyo/press/2021/12/24/21.html* (accessed September 15, 2022). (in Japanese)
10. Jonny, Violetta L, Kartasasmita AS, Amirullah Roesli RM, Rita C. Pharmacological treatment options for coronavirus disease-19 in renal patients. Int J Nephrol. 2021; 2021:4078713.
11. Hoffmann M, Krüger N, Schulz S, Cossmann A, Rocha C, Kempf A, Nehlmeier I, Graichen L, Moldenhauer AS, Winkler MS, Lier M, Dopfer-Jablonka A, Jäck HM, Behrens GMN, Pöhlmann S. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell. 2022; 185:447-456.e11.
12. The Japanese Association of Dialysis Physicians. Information. *http://www.touseki-ikai.or.jp/* (accessed September 15, 2022). (in Japanese)
13. Nishiura, H. Real-time estimation of the case fatality ratio and risk factors of death. Handbook of Statistics. 2017; 36:167-174.
14. World Health Organization. Estimating mortality from COVID-19. *https://www.who.int/news-room/commentaries/detail/estimating-mortality-from-covid-19* (accessed September 15, 2022).
15. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. *https://www.R-project.org/* (accessed September 15, 2022).
16. Tokyo Metropolitan government. COVID-19 vaccination coverage. *https://www.fukushihoken.metro.tokyo.lg.jp/iryo/kansen/coronavaccine/jisseki.html* (accessed September 12, 2022). (in Japanese)

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Real impact of oxaliplatin in adjuvant chemotherapy for patients with stage III colon cancer based on the Multi-Institutional Registry of Large Bowel Cancer in Japan

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Abstract: Although fluoropyrimidine plus oxaliplatin is the standard of care for stage III colon cancer, fluoropyrimidine alone is also recommended for stage III patients in Japanese and other practice guidelines. We assessed efficacy of adjuvant fluoropyrimidine with or without oxaliplatin across a population of patients with stage III colon cancer in the Multi-Institutional Registry of Large Bowel Cancer in Japan. From the registry, we analyzed 6,834 stage III colorectal cancer patients. Approximately 70% of colorectal cancer patients received some form of chemotherapy. Of these, we analyzed those who received adjuvant chemotherapy between 2008 and 2011. Based on the TNM classification, the 5-year overall survival rates of colon and rectal cancer after the covariate adjustment by regimens of adjuvant chemotherapy were 95.7% with fluoropyrimidines and 90.6% with oxaliplatin-combined therapy at stage IIIA (Stratified log-rank $P < 0.001$), 86.5% and 80.8% at stage IIIB ($P < 0.001$), and 72.1% and 70.7% at stage IIIC ($P < 0.001$), respectively. Oxaliplatin did not enhance efficacy with regard to relapse-free survival as well as overall survival. Adjuvant fluoropyrimidine monotherapy and fluoropyrimidine plus oxaliplatin show comparable efficacy benefits for the treatment of stage III of Japanese colon cancer patients. This supports the use of fluoropyrimidine alone as a standard option for this patient group in Japan.

***Keywords*:** real-world data, colorectal cancer, oxaliplatin, guideline, postoperative chemotherapy

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths worldwide (*1*). In Japan, there were 152,254 cases of newly diagnosed colorectal cancer in 2018, and 51,788 people died from colorectal cancer in 2020 in Japan (*2*). Postoperative adjuvant chemotherapy is given with the aim of killing any residual cancer cells to improve prognosis for cases in which R0 resection with curative intent was performed. Fluoropyrimidines and their biochemical modulation by leucovorin (LV) have been key drugs that are incorporated into treatment strategies for patients with advanced colorectal cancer at stage III and high-risk stage II (*3-5*). On the basis of results from the MOSAIC and XELOXA randomized trials, infused fluorouracil and LV with oxaliplatin (FOLFOX) and capecitabine with oxaliplatin (CapeOX) are widely used as standard postoperative adjuvant chemotherapies (*6-8*). Fluoropyrimidine plus oxaliplatin is the standard of care for stage III colon cancer but fluoropyrimidine alone is also recommended for stage III patients in Japanese and other practice guidelines (*6-9*). However, prolonged peripheral neuropathy, central venous access, and cost of care are significant problems when using oxaliplatin-based therapy (*8*).

In Japan, clinical trials of postoperative adjuvant chemotherapy have focused mainly on fluoropyrimidine-based regimens in both colon and rectal cancers because of convenient oral delivery and efficacy of the drug. Tegafur–uracil, UFT, is a combination drug comprising tegafur, a prodrug of 5-fluorouracil (5-FU) and uracil, an inhibitor of the 5-FU-degrading enzyme dihydropyrimidine dehydrogenase, in a molar ratio of 1:4. Although there were no significant differences in relapse-free survival (RFS) and overall survival (OS) in colon cancer, a benefit was observed in rectal cancer when the adjuvant UFT group and the surgery alone group were compared (*10*). A significant benefit was associated with adjuvant UFT in RFS and OS in patients with *RAS* mutation; on the other hand, there were no differences in RFS or OS between the adjuvant UFT group and surgery-alone group among patients without *RAS* mutation. The *RAS* mutation was considered predictive with respect to the efficacy of adjuvant UFT chemotherapy

in patients with resected stage III colorectal cancer (*11*). The non-inferiority of UFT/LV to 5-FU/LV as adjuvant hemotherapy for stage III colorectal cancer has been verified in both the JCOG0205 and the NSABP C-06 clinical trials (*12,13*). Therefore, UFT/LV has been widely adopted in Japan as standard adjuvant chemotherapy. S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-FU, with 2 modulators. The first is gimeracil, which reversibly inhibits DPD, the primary metabolizing enzyme of 5-FU, thereby extending the duration of 5-FU levels in the blood. The second is oteracil potassium, which reduces the activity and associated toxicity of 5-FU in gastrointestinal tissue (*14*). In the ACTS-CC trial (*15-17*), S-1 was not inferior to UFT/LV for stage III disease. Furthermore, S-1 plus oxaliplatin (SOX) was not superior to UFT/LV as adjuvant chemotherapy in the ACTS-CC02 trial (*18-20*). This latter trial focused on patients with high-risk stage III colon cancer, which is defined as N2 with any T or positive nodes around the origin of the feeding arteries. S-1 did not show non-inferiority with regard to disease-free survival (DFS) for stage III colon cancer in the JCOG0910 trial; 3-year DFS rates were 82.0% and 77.9% in the capecitabine and S-1 arms, respectively (*21*).

Here, we assessed the efficacy of adjuvant fluoropyrimidine with or without oxaliplatin across a population of stage III colon cancer patients that is present in the Japanese Multi-Institutional Registry of Large Bowel Cancer.

Methods

Patients who were diagnosed with colorectal cancer between January 1, 2008 and December 31, 2011 and were registered with the Multi-Institutional Registry of Large Bowel Cancer in Japan were enrolled in this study. Eligibility required that patients had undergone surgery for stage III colorectal cancer at a facility participating in this Registry according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus (7th edition) (*22*), and UICC TNM classification (7th edition) (*23*).

Pearson's chi-square test was used to determine whether there were differences between proportions. Survival functions for OS and RFS were estimated by the Kaplan-Meier method, and confidence intervals (CI) were calculated based on the Greenwood formula. The confidence intervals of median survival time were calculated using the Brookmeyer-Crowley method. Adjusted survival functions for OS and RFS were calculated based on the conditional method (*24*). Hazard ratio (HR) and adjusted HR for OS and RFS were obtained using Cox regression models. Competing risk analysis was performed to account for the impact of death due to other diseases. Death due to other diseases was treated as a competing risk event, and adjusted sub distribution HRs were calculated using the Fine–Gray model. Possible prognostic factors (*i.e.*, age, sex, histologic type, stage, pre-serum carcinoembryonic antigen (CEA), location, and postoperative chemotherapy) were adjusted in multivariable analyses as appropriate. The cut-off value of age was due to the definition of older age in Japan, and that of CEA was the normal upper limit value. This study was approved by the certified review boards.

A two-sided *P*-value < 0.05 was considered to be significant. R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) with gtsummary packge (*25*) was used for all statistical analyses.

Results

Data from 26,552 patients with colorectal cancer at 67 hospitals in Japan were collected; 6,843 patients at stage III were analyzed in this study (Figure 1). Median follow-up was 74.9 months in the oxaliplatin combined therapy group and 74.7 months in the fluoropyrimidine monotherapy group. Fluoropyrimidines consisted of 5-FU/*l*-leucovorin (*l*-LV), capecitabine, UFT/LV, and S-1. The oxaliplatin-combined regimen was oxaliplatin plus 5-FU/*l*-LV. Others included UFT, irinotecan plus 5-FU/*l*-LV, capecitabine plus oxaliplatin, and S-1 plus oxaliplatin. Infusional 5-FU/*l*-LV/oxaliplatin combination therapy (FOLFOX) was recommended as adjuvant chemotherapy in the JSCCR guidelines 2010 (*26*) for the treatment of colorectal cancer and – consistent with the 2009 version (*27*) – FOLFOX was not reimbursed by insurance.

The 5-, 7-, and 10-year OS rates were 75.9%, 68.3%, and 62.6%, and the 3-year, 5-, 7-, and 10-year RFS rates were 68.9%, 63.0%, 58.5%, and 54.0%, respectively (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). The right colon consisted of cecum, C, and ascending, A, and transverse colon, T. The left colon consisted of descending colon, D, and sigmoid colon, S. The rectum was divided into rectosigmoid, RS, rectum above the peritoneal reflection, Ra, and rectum below the peritoneal reflection, Rb, as in the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, the 7th edition by Japanese Society for Cancer of the Colon. The 5-year OS rates in right

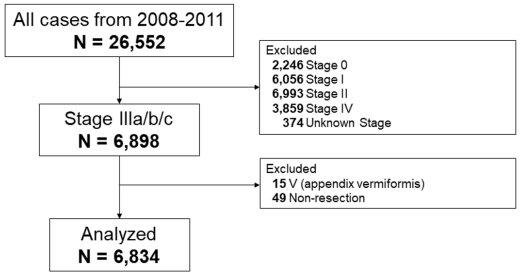


Figure 1. Flow diagram of the patient selection process.

colon (*N* = 1,892), left colon (*N* = 1,911), and rectum (*N* = 2,864) were 74.2%, 78.4%, and 76.3%, respectively (Figure 2).

Approximately 30% of colorectal cancer patients received some form of chemotherapy. The mean age of patients without adjuvant chemotherapy (73 years) was higher than that of those treated with Fluoropyrimidine monotherapy (64 years) and those treated with an oxaliplatin-combined regimen (61 years; Table 1). The proportions of death due to other disease were 30% in the no adjuvant chemotherapy group, 16% in the Fluoropyrimidine monotherapy group, and 10% in the oxaliplatin-combined regimen group (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). The RFS rates in the right colon, left colon, and rectum were 66.1%, 65.8%, and 60.1%, respectively. Postoperative adjuvant chemotherapy was effective in all locations (Table 2).

The 5-year OS rates associated with colon and rectal cancer were 90.2% and 93.1% at stage IIIa, 78.2% and 78.2% at stage IIIb, 67.0% and 60.2% at stage IIIc, respectively (Figure 3). Factors associated with a significantly worse prognosis for OS were age 65 or more, male, rectal site, poorly differentiated adenocarcinoma (por)/mucinous adenocarcinoma (muc)/signet-ring cell carcinoma (sig)/others. For RFS, the factors were male, rectal site, and serum CEA level of 5 ng/mL or more at baseline in RFS (Table 3). Patients not treated with any adjuvant chemotherapy tended to be older and generally had colon cancer. T4 or N2 patients and stage IIIc patients were treated with oxaliplatin (Table 4). The 5-year OS rates associated with colon and rectal cancer after the

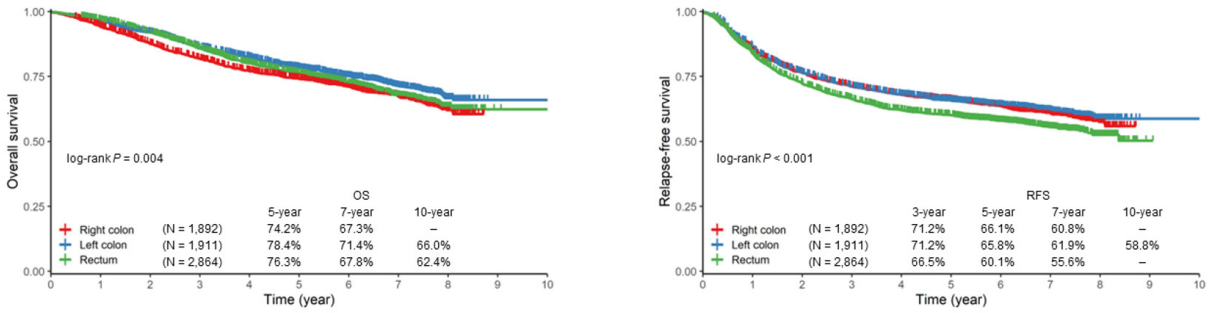


Figure 2. Overall survival (OS) and relapse-free survival (RFS) of colorectal cancer at stage III by primary lesion. Right colon; C, cecum, A, ascending, and T, transverse colon: left colon; D, descending and S, sigmoid colon: rectum; RS, rectosigmoid, Ra, rectum above the peritoneal reflection, and Rb, rectum below the peritoneal reflection.

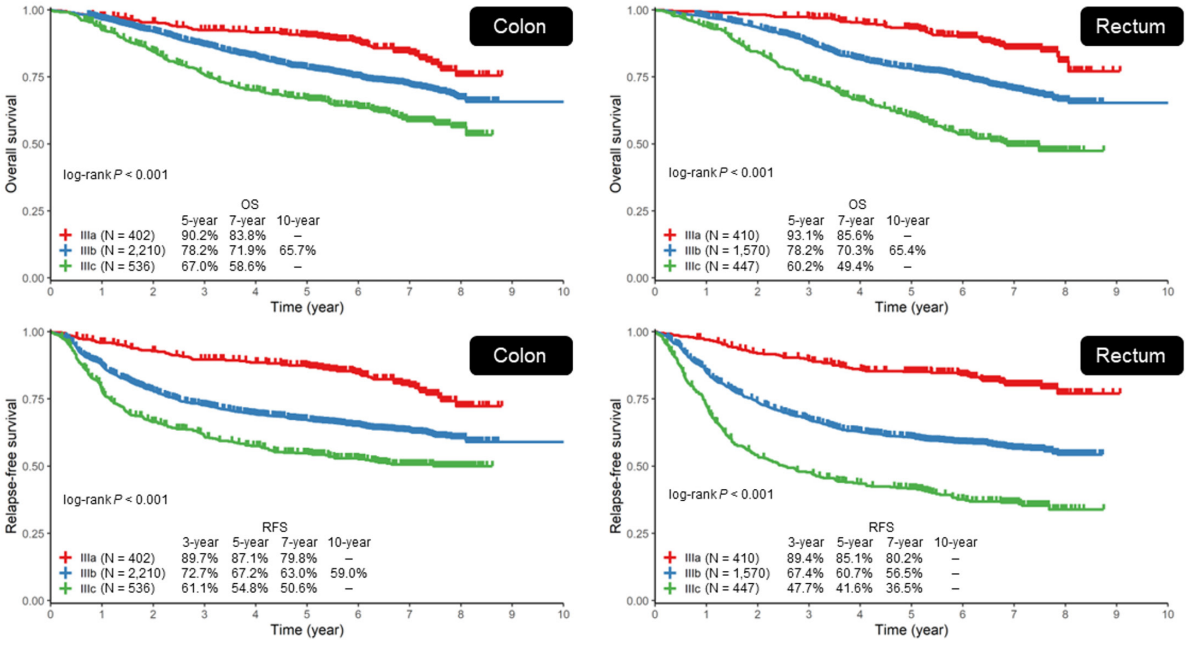


Figure 3. Overall survival (OS) and relapse-free survival (RFS) of colorectal cancer at stage III by Japanese classification. Colon; C, cecum, A, ascending, and T, transverse colon, D, descending and S, sigmoid colon: rectum; RS, rectosigmoid, Ra, rectum above the peritoneal reflection, and Rb, rectum below the peritoneal reflection.

Table 1. Patient characteristics

Variable	All, *N* = 6,834	Right colon, *N* = 1,892	Left colon, *N* = 1,911	Rectum, *N* = 2,864	Variable	All, *N* = 6,834
Sex					Right colon	
Male	3,846 (56%)	892 (47%)	1,072 (56%)	1,786 (62%)	C, cecum	468 (7.0%)
Female	2,988 (44%)	1,000 (53%)	839 (44%)	1,078 (38%)	A, ascending colon	889 (13%)
Age, mean (SD)	67 (12)	70 (11)	66 (12)	65 (12)	T, transverse colon	535 (8.0%)
Adjuvant chemotherapy					Left colon	
No adjuvant chemotherapy	1,935 (30%)	618 (35%)	556 (31%)	717 (27%)	D, descending colon	266 (4.0%)
Preoperative radiotherapy	121 (1.9%)	0 (0%)	2 (0.1%)	112 (4.2%)	S, sigmoid colon	1,645 (24%)
Postoperative radiotherapy	49 (0.8%)	5 (0.3%)	11 (0.6%)	29 (1.1%)	Rectum	
Preoperative chemotherapy	164 (2.6%)	12 (0.7%)	7 (0.4%)	135 (5.1%)	RS, rectosigmoid junction	908 (13%)
Postoperative chemotherapy	4,303 (68%)	1,139 (64%)	1,224 (68%)	1,853 (70%)	Ra, rectum above the peritoneal reflection	914 (14%)
Any adjuvant therapy	11 (0.2%)	6 (0.3%)	3 (0.2%)	1 (< 0.1%)	Rb, rectum below theperitoneal reflection	1,042 (15%)
Postoperative chemotherapy					P, proctos	60 (0.9%)
Fluoropyrimidine monotherapy	2,719 (76%)	752 (80%)	800 (79%)	1,124 (73%)	Colon/rectum	
Oxaliplatin combined therapy	514 (14%)	120 (13%)	132 (13%)	251 (16%)	Colon	3,803 (57%)
Others	329 (9.2%)	71 (7.5%)	85 (8.4%)	163 (11%)	Rectum	2,864 (43%)

N (%) or Mean (SD) are shown. Primary region was unknown in107 patients.

Table 2. The effect of adjuvant chemotherapy by location of primary colorectal cancer at stage III

Location/Treatment	*N*	OS						RFS					
		HR	95% CI	*P*-value	Adj. HR*	95% CI	*P*-value	HR	95% CI	*P*-value	Adj. HR*	95% CI	*P*-value
Colon													
No adjuvant chemotherapy	896	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,320	0.35	0.30, 0.41	< 0.001	0.35	0.30, 0.42	< 0.001	0.49	0.42, 0.56	< 0.001	0.50	0.43, 0.58	< 0.001
Oxaliplatin combined therapy	202	0.55	0.43, 0.72	< 0.001	0.44	0.33, 0.60	< 0.001	0.78	0.63, 0.97	0.024	0.64	0.50, 0.83	< 0.001
Others	132	0.77	0.58, 1.02	0.067	0.78	0.58, 1.06	0.114	0.92	0.72, 1.19	0.533	0.98	0.75, 1.28	0.895
Right colon													
No adjuvant chemotherapy	465	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	641	0.30	0.24, 0.38	< 0.001	0.30	0.24, 0.38	< 0.001	0.42	0.34, 0.52	< 0.001	0.42	0.34, 0.52	< 0.001
Oxaliplatin combined therapy	97	0.52	0.37, 0.74	< 0.001	0.41	0.27, 0.62	< 0.001	0.72	0.53, 0.98	0.034	0.63	0.44, 0.89	0.009
Others	59	0.59	0.38, 0.91	0.018	0.65	0.41, 1.04	0.071	0.71	0.48, 1.06	0.092	0.78	0.51, 1.18	0.243
Left colon													
No adjuvant chemotherapy	431	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	679	0.41	0.33, 0.52	< 0.001	0.44	0.34, 0.56	< 0.001	0.57	0.47, 0.69	< 0.001	0.60	0.49, 0.74	< 0.001
Oxaliplatin combined therapy	105	0.60	0.41, 0.88	0.008	0.51	0.32, 0.81	0.004	0.85	0.63, 1.16	0.310	0.69	0.48, 1.00	0.049
Others	73	1.00	0.69, 1.45	0.995	0.95	0.63, 1.42	0.802	1.16	0.83, 1.62	0.381	1.20	0.84, 1.70	0.321
Rectum													
No adjuvant chemotherapy	635	Reference			Reference			Reference			Reference		
Fluoropyrimidine monotherapy	981	0.38	0.32, 0.45	< 0.001	0.38	0.32, 0.47	< 0.001	0.59	0.51, 0.68	< 0.001	0.58	0.49, 0.68	< 0.001
Oxaliplatin combined therapy	215	0.48	0.36, 0.63	< 0.001	0.38	0.28, 0.52	< 0.001	0.73	0.58, 0.91	0.006	0.58	0.45, 0.74	< 0.001
Others	130	0.60	0.43, 0.82	0.002	0.52	0.37, 0.74	< 0.001	0.76	0.58, 0.99	0.042	0.65	0.49, 0.87	0.004

*HRs were adjusted by age, sex, histologic type, stage, and Pre CEA. OS, overall survival; RFS, relapse-free survival.

Table 3. Multivariable analyses of patients with colorectal cancer at stage III (*N* = 2,718)

Variable	OS (univariable)			OS (Multivariable)			RFS (univariable)			RFS (Multivariable)		
	HR	95% CI	*P*-value	Adj. HR	95% CI	*P*-value	HR	95% CI	*P*-value	Adj. HR	95% CI	*P*-value
Postoperative chemotherapy												
Fluoropyrimidine monotherapy	Reference			Reference			Reference			Reference		
Oxaliplatin combined therapy	1.43	1.18, 1.73	< 0.001	1.11	0.88, 1.38	0.380	1.43	1.22, 1.67	< 0.001	1.14	0.96, 1.36	0.139
Age												
< 65	Reference			Reference			Reference			Reference		
≥ 65	1.25	1.07, 1.46	0.006	1.36	1.14, 1.62	< 0.001	0.96	0.85, 1.09	0.568	1.04	0.91, 1.18	0.611
Sex												
Male	Reference			Reference			Reference			Reference		
Female	0.86	0.74, 1.01	0.068	0.83	0.70, 0.99	0.040	0.81	0.71, 0.92	< 0.001	0.79	0.69, 0.90	< 0.001
Colon/Rectum												
Colon	Reference			Reference			Reference			Reference		
Rectum	1.09	0.93, 1.27	0.311	1.21	1.02, 1.44	0.032	1.33	1.17, 1.50	< 0.001	1.41	1.24, 1.62	< 0.001
Histologic Type												
well/mod	Reference			Reference			Reference			Reference		
por/muc/sig/others	2.00	1.63, 2.47	< 0.001	1.47	1.15, 1.88	0.002	1.51	1.26, 1.81	< 0.001	1.18	0.96, 1.45	0.110
Stage												
IIIa	Reference			Reference			Reference			Reference		
IIIb	2.30	1.65, 3.21	< 0.001	2.36	1.65, 3.38	< 0.001	2.67	2.05, 3.47	< 0.001	2.78	2.10, 3.68	< 0.001
IIIc	4.57	3.22, 6.49	< 0.001	4.45	3.03, 6.53	< 0.001	4.58	3.46, 6.06	< 0.001	4.38	3.23, 5.93	< 0.001
Pre CEA												
< 5 ng/mL	Reference			Reference			Reference			Reference		
≥ 5 ng/mL	1.43	1.13, 1.79	0.002	1.19	0.92, 1.52	0.183	1.63	1.36, 1.95	< 0.001	1.39	1.14, 1.68	< 0.001

OS, overall survival; RFS, relapse-free survival, well, well differentiated tubular adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma; pre CEA, pre-serum carcinoembryonic antigen.

covariate adjustment were 94.4% and 96.8% at stage IIIa, 86.5% and 85.7% at stage IIIb, 78.9% and 67.2% at stage IIIc by Japanese classification, respectively (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*).

The 5-year OS rates associated with colon and rectal cancer after the covariate adjustment by regimens of adjuvant chemotherapy were 95.7% with fluoropyrimidines and 96.8% with oxaliplatin-combined therapy at stage IIIA, 86.5% and 80.8% at stage IIIB, 72.1% and 70.7% at stage IIIC by the TNM classification, respectively (Figure 4). No additive effect of oxaliplatin was observed in stage III patients with any T, N1 or N2; this is consistent with results in the equivalent target population in the "MOSAIC" trial (Figure 5, Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). Fluoropyrimidine monotherapy was more effective than oxaliplatin-combined regimen in colon cancer patients with N1 (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=55*). Oral capecitabine imparted statistically significant benefit in OS and RFS compared with oral UFT/ LV (Figure 6).

Discussion

Adjuvant fluoropyrimidine monotherapy and fluoropyrimidine plus oxaliplatin show comparable efficacy benefits for the treatment of stage III of Japanese colon cancer patients, supporting fluoropyrimidine alone as a standard option for the adjuvant therapy of stage III cancer in Japan. Thirty percent of stage III colorectal cancer patients did not receive any adjuvant chemotherapy. We recommend that elderly patients with other concomitant diseases should not be given adjuvant chemotherapy.

In the ACTS-CC02 study, S-1 plus oxaliplatin therapy (SOX) was not superior to UFT/LV in terms of OS and disease-free survival (DFS) in patients with high-risk stage III colon cancer of any T, N2, or positive nodes around the origin of the feeding arteries (*18,20*). SOX was efficacious in patients with T4N2b disease. However, oxaliplatin-combined regimen was not superior to fluoropyrimidines in our real-world data even in the T4 population with or without N2b. The mean relative dose intensity (RDI) was 83.1% for UFT, 74.9% for S-1 and 73.6% for oxaliplatin in SOX in ACTS-CC02 (*20*). The RDI of S-1 in SOX therapy was similar to the 76.5% of RDI with S-1 monotherapy and 76.0% with UFT in ACTS-CC study, which showed the non-inferiority of S-1 to UFT/LV for stage III colon cancer (*16*). Therefore, oxaliplatin did not significantly reduce the RDI of S-1 in the SOX group. The additive effect of oxaliplatin was not shown in the unique randomized controlled trial of ACTS-CC02 in Japan.

ACHIEVE was a Japanese phase III trial that explored whether 3 months of adjuvant FOLFOX or CapeOX therapy was non-inferior to 6 months of treatment in patients with stage III colon cancer (*24-26*). The 5-year OS rates were 79.8% in the 3-months oxaliplatin-combined regimen group and 79.8% in the 6-month group in high-risk disease patients with T4 or N2 (*26*). Patients with CAPOX were significantly more likely to develop adverse events of grade 3 or more when they had a baseline creatinine clearance (CCr) less than 50 mL/

Table 4. Frequency of adjuvant chemotherapy

	Male *N* = 3,846	Female *N* = 2,988		*P*-value*	Age: ≤ 59 *N* = 1,674	Age: 60-69 *N* = 2,234	Age: 70-79 *N* = 1,973	Age: ≥ 80 *N* = 953	*P*-value*
Treatment				0.063					< 0.001
No adjuvant chemotherapy	1,155 (36.7%)	888 (36.1%)			261 (19.7%)	464 (25.5%)	646 (39.3%)	672 (82.2%)	
Fluoropyrimidine monotherapy	1,485 (47.2%)	1,234 (50.1%)			761 (57.5%)	1,063 (58.5%)	779 (47.4%)	116 (14.2%)	
Oxaliplatin combined therapy	309 (9.8%)	205 (8.3%)			210 (15.9%)	181 (10.0%)	117 (7.1%)	6 (0.7%)	
Others	195 (6.2%)	134 (5.4%)			92 (6.9%)	110 (6.1%)	103 (6.3%)	24 (2.9%)	
	Colon *N* = 3,803	Rectum *N* = 2,864		*P*-value*	T1-2 *N* = 1,076	T3 *N* = 3,786	T4 *N* = 1,842		*P*-value*
Treatment				< 0.001					< 0.001
No adjuvant chemotherapy	1,203 (38.0%)	789 (33.9%)			296 (34.4%)	1,162 (37.3%)	534 (35.0%)		
Fluoropyrimidine monotherapy	1,552 (49.1%)	1,124 (48.3%)			470 (54.6%)	1,501 (48.2%)	717 (47.0%)		
Oxaliplatin combined therapy	252 (8.0%)	251 (10.8%)			52 (6.0%)	284 (9.1%)	169 (11.1%)		
Others	156 (4.9%)	163 (7.0%)			43 (5.0%)	169 (5.4%)	107 (7.0%)		
	N1 *N* = 4,235	N2a *N* = 992	N2b *N* = 637	*P*-value*		IIIa *N* = 827	IIIb *N* = 3,842	IIIc *N* = 1,020	*P*-value*
Treatment				< 0.001					< 0.001
No adjuvant chemotherapy	1,339 (36.7%)	232 (27.8%)	146 (26.6%)			238 (33.7%)	1,185 (35.9%)	266 (30.5%)	
Fluoropyrimidine monotherapy	1,879 (51.4%)	428 (51.2%)	228 (41.5%)			400 (56.7%)	1,675 (50.7%)	382 (43.9%)	
Oxaliplatin combined therapy	226 (6.2%)	127 (15.2%)	135 (24.6%)			32 (4.5%)	250 (7.6%)	164 (18.8%)	
Others	209 (5.7%)	49 (5.9%)	40 (7.3%)			36 (5.1%)	192 (5.8%)	59 (6.8%)	

*Pearson's Chi-squared test.

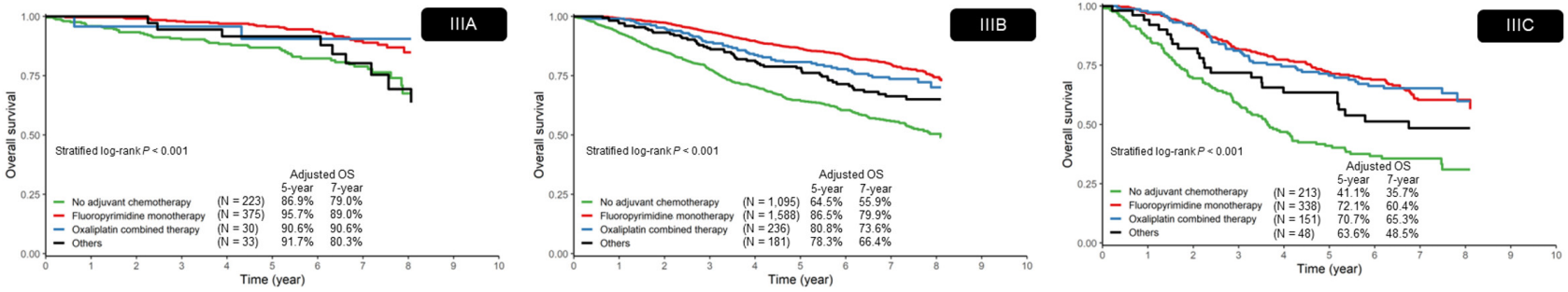
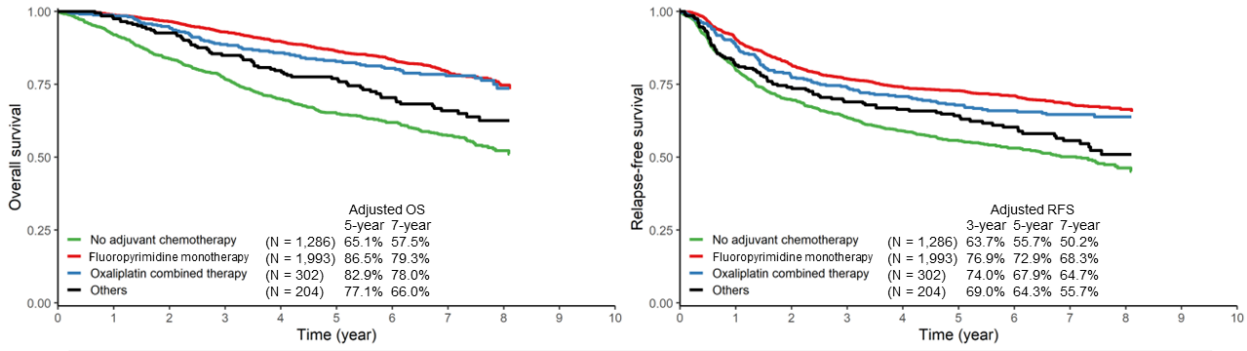


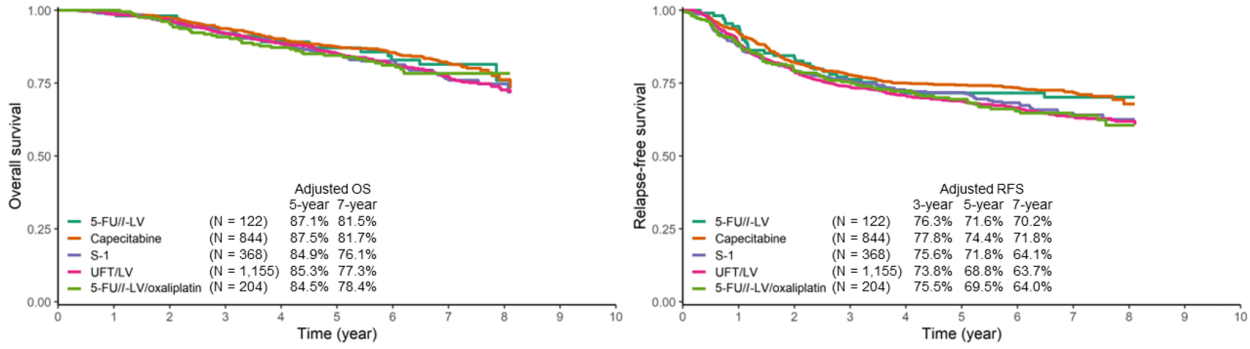
Figure 4. Overall survival (OS) of Stage IIIA/IIIB/IIIC colorectal cancer by the TNM classification after the covariate adjustment.



Treatment	N		OS HR	OS 95% CI	OS *P*-value	OS (competing risk analysis#) HR	OS (competing risk analysis#) 95% CI	OS (competing risk analysis#) *P*-value	RFS HR	RFS 95% CI	RFS *P*-value
No adjuvant chemotherapy	1,286	Crude	Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,993		0.34	0.30, 0.39	< 0.001	0.45	0.39, 0.52	< 0.001	0.51	0.45, 0.56	< 0.001
Oxaliplatin combined therapy	302		0.50	0.40, 0.62	< 0.001	0.70	0.55, 0.88	< 0.001	0.73	0.61, 0.88	< 0.001
Others	204		0.65	0.51, 0.83	< 0.001	0.84	0.64, 1.09	0.188	0.86	0.67, 1.02	0.074
No adjuvant chemotherapy	1,286	Adjusted*	Reference			Reference			Reference		
Fluoropyrimidine monotherapy	1,993		0.36	0.31, 0.42	< 0.001	0.46	0.39, 0.54	< 0.001	0.53	0.47, 0.59	< 0.001
Oxaliplatin combined therapy	302		0.41	0.31, 0.52	< 0.001	0.53	0.40, 0.70	< 0.001	0.61	0.50, 0.75	< 0.001
Others	204		0.66	0.50, 0.85	0.002	0.82	0.61, 1.09	0.170	0.83	0.66, 1.04	0.107

* HRs were adjusted by age, sex, location, histologic type, stage, and pre-serum carcinoembryonic antigen.
# Death due to other diseases was treated as a competing risk event, and the Fine-Gray model was used for analysis.

Figure 5. Overall survival (OS) and relapse-free survival (RFS) at stage III colon cancer with any T, N1 or N2 by the TNM classification.



Treatment	N		OS HR	OS 95% CI	OS *P*-value	RFS HR	RFS 95% CI	RFS *P*-value
Capecitabine	122	Crude	Reference			Reference		
5-FU//-LV	844		0.99	0.63, 1.57	0.980	1.20	0.85, 1.68	0.315
S-1	368		1.34	1.02, 1.76	0.034	1.34	1.07, 1.66	0.009
UFT/LV	1,155		1.28	1.04, 1.58	0.018	1.39	1.18, 1.64	<0.001
5-FU//-LV/oxaliplatin	204		1.51	1.09, 2.07	0.012	1.68	1.31, 2.15	<0.001
Capecitabine	122	Adjusted*	Reference			Reference		
5-FU//-LV	844		1.03	0.62, 1.69	0.917	1.05	0.72, 1.53	0.782
S-1	368		1.26	0.94, 1.69	0.129	1.27	1.01, 1.60	0.044
UFT/LV	1,155		1.26	1.01, 1.57	0.044	1.32	1.11, 1.57	0.002
5-FU//-LV/oxaliplatin	204		1.16	0.80, 1.66	0.440	1.33	1.01, 1.75	0.045

* HRs were adjusted by age, sex, location, histologic type, stage, and Pre CEA

Figure 6. Overall survival (OS) and relapse-free survival (RFS) of stage III colorectal cancer by regimen. 5-FU, 5-fluorouracil; *l*-LV, *l*-leucovorin; UFT, tegafur-uracil ; LV, leucovorin.

min (*24*). Based on this, we amended the protocol and added a CCr of more than 30 mL/min to the eligibility criteria; the CapeOX regimen was then initiated with a decreased dose of capecitabine of 1,500 mg/m^2 from 2,000 mg/m^2 per day in patients with a CCr of 30 to 50 mL/min and/or who were > 70 years old. The combination with oxaliplatin compromised the maximum tolerated dose of capecitabine due to toxicity. Therefore, caution should be exercised when interpreting the results of this clinical trial, particularly those related to the combination of oxaliplatin as adjuvant chemotherapy. We observed a significant efficacy of fluoropyrimidine monotherapy in this Japanese real-world study. Capecitabine was superior to S-1 for stage III patients in the previous JCOG0910 study (*21*). This drug also seemed to be more effective than UFT/LV, S-1, 5-FU/ *l*-LV/ oxaliplatin therapy in our current study, which used real world data (Figure 6).

Based on the results of previous adjuvant trials, oxaliplatin-combined regimens are considered standard adjuvant chemotherapy for patients with stage III colon cancer especially in Western countries. On the other hand, fluoropyrimidine monotherapies elicit favorable results when used as adjuvant chemotherapy in Japan, and are comparable to oxaliplatin-combined regimens that are used in Western countries. There are two factors that may contribute to a better outcome: D3 lymph node dissection

and thorough pathological examinations (*28-30*). Standard colon cancer surgery in the West employs resection of a long portion of the colon with limited central lymph node dissection (*31*). On the other hand, in Japan, resection of a shorter section of the colon is accompanied by extensive lymph node dissection in the central direction (D3 lymph node dissection) (*32*). Therefore, the physical location of the dissected lymph nodes is quite different in the two geographic locations, even if the number of dissected lymph nodes is similar (*33*). In the West, lymph nodes are removed from excised specimens, fixed with formalin and submitted for pathological examination. However, in Japan lymph nodes are removed from fresh excised specimens before formalin fixation and submitted for pathological examination after formalin fixation. Studies of large numbers of colon cancer patients from Japan and the United States revealed that 12 or more lymph nodes were examined in 68% and 37% of patients, respectively (*34,35*). Such differences in the frequency with which a given number of lymph nodes are examined may contribute to stage migration. Therefore, extrapolating the results from trials of adjuvant chemotherapy in Europe and the United States to the situation in Japan is not appropriate. Rather, clinical evidence based on Japanese surgery and pathological examination data should be used to guide treatment of patients in Japan.

In conclusion, adjuvant chemotherapy using fluoropyrimidines without oxaliplatin for stage III colorectal cancer elicited a significant effect on OS. Fluoropyrimidine monotherapy should be chosen for many Japanese colorectal cancer patients based on our analysis of real-world big data. Optimal chemotherapy in the adjuvant setting for colorectal cancer should therefore be chosen based on the medical environment in each country.

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References

1. Sung H, Ferlay J, Siegel RL, Mathieu Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185. CA Cancer J Clin. 2021; 71:209-249.
2. Ganjoho Service. Totalization tables. *https://ganjoho.jp/reg_stat/statistics/data/dl/index.html#a14* (accessed June 10, 2022). (in Japanese)
3. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. Cancer. 1989; 63 (6 Suppl):1026-1030.
4. E Jäger, M Heike, H Bernhard, O Klein, G Bernhard, D Lautz, J Michaelis, K H Meyer zum Büschenfelde, A Knuth. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol. 1996; 14:2274-2279.
5. A Sobrero, G Frassineti, A Falcone, L Dogliotti, R Rosso, F Di Costanzo, P Bruzzi, INTACC. Adjuvant sequential methotrexate → 5-fluorouracil *vs* 5-fluorouracil plus leucovorin in radically resected stage III and high-risk stage II colon cancer. Br J Cancer. 2005; 92:24-29.
6. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004; 350:2343-2351.
7. Schmoll HJ, Twelves C, Sun W, O'Connell MJ, Cartwright T, McKenna E, Saif M, Lee S, Yothers G, Haller D. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. Lancet Oncol. 2014; 15:1481-1492.
8. Grothey A, Sobrero AF, Shields T, *et al.* Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med. 2018; 378:1177-1188.
9. Kuebler JP, Wieand HS, O'Connell MJ, *et al.* Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007; 25:2198-2204.
10. Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y; NSAS-CC Group. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol. 2011; 67:587-596.
11. Sasaki Y, Akasu T, Saito N, Kojima H, Matsuda K, Nakamori S, Komori K, Amagai K, Yamaguchi T, Ohue M, Nagashima K, Yamada Y. Prognostic and predictive value of extended RAS mutation and mismatch repair status in stage III colorectal cancer. Cancer Sci. 2016; 107:1006-1012.
12. Shimada Y, Hamaguchi T, Mizusawa J, *et al.* Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil

and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer. 2014; 50:2231-2240.
13. O'Connell MJ, Lavery I, Yothers G, Paik S, Clark-Langone KM, Lopatin M, Watson D, Baehner FL, Shak S, Baker J, Cowens JW, Wolmark N. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. J Clin Oncol. 2010; 28:3937-3944.
14. Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A, Saito H, Okabe H, Oyama K, Takeda S, Unemi N, Fukushima M. Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res. 1996; 56:2602-2606.
15. Yoshida M, Ishiguro M, Ikejiri K, *et al.* S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol. 2014; 25:1743-1749.
16. Mochizuki I, Takiuchi H, Ikejiri K, *et al.* Safety of UFT/LV and S-1 as adjuvant therapy for stage III colon cancer in phase III trial: ACTS-CC trial. Br J Cancer. 2012; 106:1268-1273.
17. Kusumoto T, Ishiguro M, Nakatani E, *et al.* Updated 5-year survival and exploratory T x N subset analyses of ACTS-CC trial: a randomised controlled trial of S-1 versus tegafur-uracil/leucovorin as adjuvant chemotherapy for stage III colon cancer. ESMO Open. 2018; 3:e000428.
18. Sunami E, Kusumoto T, Ota M, *et al.* S-1 and oxaliplatin versus tegafur-uracil and leucovorin as postoperative adjuvant chemotherapy in patients with high-risk stage III colon cancer (ACTS-CC 02): A randomized, open-label, multicenter, phase III superiority trial. Clin Colorectal Cancer. 2020; 19:22-31.
19. Kusumoto T, Sunami E, Ota M, *et al.* Planned safety analysis of the ACTS-CC 02 Trial: A randomized phase III trial of S-1 with oxaliplatin versus tegafur and uracil with leucovorin as adjuvant chemotherapy for high-risk stage III colon cancer. Clin Colorectal Cancer. 2018; 17:e153-e161.
20. Watanabe J, Sasaki S, Kusumoto T, *et al*. S-1 and oxaliplatin versus tegafur-uracil and leucovorin as post-operative adjuvant chemotherapy in patients with high-risk stage III colon cancer: updated 5-year survival of the phase III ACTS-CC 02 trial. ESMO Open. 2021; 6:100077.
21. Hamaguchi T, Shimada S, Mizusawa J, *et al.* Capecitabine versus S-1 as adjuvant chemotherapy for patients with stage Ill colorectal cancer (JCOG0910): an open-label, non-inferiority, randomised, phase 3, multicentre trial. Lancet Gastroenterol Hepatol. 2018; 3:47-56.
22. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 3rd English Edition, April 2019. *http://jsccr.jp/kiyaku/files/kiyaku_en_02.pdf* (accessed June 10, 2022).
23. Edge SB, Byrd SR, Compton CC, *et al.* AJCC Cancer Staging Manual. 7th edition Springer-Verlag; New York (NY): 2010. pp. 143-164.
24. Nieto FJ, Coresh J. Adjusting survival curves for confounders: a review and a new method. Am J Epidemiol. 1996; 143:1059-1068.
25. Sjoberg DD, Whiting K, Curry M, Lavery JA, Larmarange J. Reproducible summary tables with the gtsummary package. The R Journal. 2021; 13:570-580.
26. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *http://www.jsccr.jp/guideline/2010/particular.html* (accessed June 10, 2022). (in Japanese)
27. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2009 for the treatment of colorectal cancer. *http://www.jsccr.jp/guideline/2009/particular.html* (accessed June 10, 2022). (in Japanese)
28. Kotaka M, Yamanaka T, Yoshino T, *et al.* Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer. ESMO Open. 2018; 3:e000354.
29. Yoshino T, Yamanaka T, Oki E, *et al.* Efficacy and long-term peripheral sensory neuropathy of 3 *vs* 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: The ACHIEVE phase 3 randomized clinical trial. JAMA Oncol. 2019; 5:1574-1581.
30. Yoshino T, Oki E, Misumi T, *et al*. Final analysis of 3 versus 6 months of adjuvant oxaliplatin and fluoropyrimidine-based therapy in patients with stage III colon cancer: The Randomized Phase III ACHIEVE Trial. J Clin Oncol. 2022; JCO2102628.
31. Kobayashi H, West NP, Takahashi K, Perrakis A, Weber K, Hohenberger W, Quirke P, Sugihara K. Quality of surgery for stage III colon cancer: comparison between England, Germany, and Japan. Ann Surg Oncol. 2014; 21 Suppl 3:S398-S404.
32. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, Sugihara K, Quirke P. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol. 2012; 30:1763-1769.
33. Ishiguro M, Watanabe T, Kotake K, Sugihara K. Japanese Society for Cancer of the Colon and Rectum Guidelines 2010 for the treatment of colorectal cancer: comparison with Western guidelines. Colorect Cancer. 2013; 2:179-190.
34. Kotake K, Mizuguchi T, Moritani K, Wada O, Ozawa H, Oki I, Sugihara K. Impact of D3 lymph node dissection on survival for patients with T3 and T4 colon cancer. Int J Colorectal Dis. 2014; 29:847-852.
35. Bilimoria KY, Bentrem JB, Stewart AK, Talamonti MS, Winchester DP, Russell TR, Ko CY. Lymph node evaluation as a colon cancer quality measure: a national hospital report card. J Natl Cancer Inst. 2008; 100:1310-1317.

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Physician practices in the diagnosis and treatment of infectious diseases in home care settings: A questionnaire study

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Abstract: To elucidate the current practices of infectious disease management in home care settings in Japan, we sent a questionnaire to 36 physicians working at 13 clinics that specialize in providing care to patients in their homes or residential care facilities. The questionnaire described three hypothetical scenarios (aspiration pneumonia, pyelonephritis, and neoplastic fever) in older patients with terminal cancer, and 25 respondents answered questions on testing and treatment strategies. Most respondents chose to obtain cultures for aspiration pneumonia (sputum) and for pyelonephritis (urine), although fewer respondents chose to obtain blood cultures. For neoplastic fever, most of respondents elected to continue observation without antibiotic treatment. The most frequently selected antibiotics were cephalosporins and quinolones. The results indicated that most respondents would perform bacterial culture tests before prescribing antibiotics and observe patients when bacterial infections are not suspected. Standardized guidelines are needed to optimize infectious disease management in home care.

***Keywords*:** home care service, antimicrobial stewardship, antibiotic resistance, physician practice pattern

Introduction

Due to an exceptionally long-life expectancy and low birth rate, Japan has become the world's most super-aged country with 28.4% of its population aged ≥ 65 years in 2019 (*1*). This population aging will be accompanied by an increasing number of functionally impaired older persons with difficulty in regularly visiting health facilities to receive care. The Ministry of Health, Labour and Welfare of Japan is promoting home care as part of overarching efforts toward realizing regional medical care goals and developing community-based integrated care systems (*2*). Accordingly, home care will play an increasingly prominent role in Japan's healthcare system.

Infectious diseases are among the most frequently encountered health problems in older persons living at home (*3*). The minimization of preventable hospitalizations can help to contain rising healthcare costs and resource consumption in an aging population. Although it is important for home care service providers to link with hospitals when necessary, a previous study reported that approximately 80% of older patients with infection-induced fever were successfully treated at home (*4*). This indicates that the home-based management of infections is a potentially important element in reducing hospitalizations. However, widespread overuse of antibiotics can lead to increases in adverse events and antibiotic resistance, thereby causing harm to both patients and society (*5*). For example, a recent study reported that antibiotic-resistant bacteria were detected in 24 (14.9%) of 161 older persons receiving home care in Okinawa (*6*). The quantity of antibiotics administered at home is likely to rise as home care services become more prevalent, resulting in a growing need to apply antimicrobial stewardship practices in home care settings.

Despite the need to ensure appropriate infectious disease management in home care, little is known about these current practices in Japan. Therefore, we conducted a questionnaire study to elucidate the testing and treatment strategies of home care physicians for suspected infections in older patients.

Study design and information collection

Study subjects: We conducted a questionnaire study targeting 36 physicians providing home care between

Table 1. Selected tests in each scenario (*n* = 25)

Selected tests	Own-home care	Residential care
Scenario 1 (Suspected aspiration pneumonia)		
Obtain past bacterial culture results	16 (64.0)	15 (60.0)
Sputum culture	19 (76.0)	20 (80.0)
Blood culture	8 (32.0)	8 (32.0)
Scenario 2 (Suspected pyelonephritis)		
Obtain past bacterial culture results	11 (44.0)	11 (44.0)
Urine culture	19 (76.0)	19 (76.0)
Blood culture	10 (40.0)	10 (40.0)
Scenario 3 (Suspected neoplastic fever)		
Obtain past bacterial culture results	11 (44.0)	11 (44.0)
Sputum culture	9 (36.0)	9 (36.0)
Urine culture	6 (24.0)	6 (24.0)
Blood culture	7 (28.0)	7 (28.0)

Values are presented as *n* (%).Own-home care refers to care provided to patients living at home, whereas residential care refers to care provided to patients living at a residential facility.

June 20 and August 19, 2018. The physicians were employed by 13 clinics operated by the Yushoukai Medical Corporation (Tokyo, Japan). These clinics specialize in providing home care within the Greater Tokyo Area, and offer a wide variety of home-based treatments such as pediatric care, chronic disease management, cancer care, and geriatric care.

Questionnaire: We developed a questionnaire to gather information on the respondents' testing and treatment strategies for hypothetical patient scenarios. Although there is a wide variety of baseline characteristics and underlying diseases among home care patients, our scenarios focused on older patients with terminal cancer. First, the questionnaire collected information on the following respondent characteristics: number of years since graduation, medical specialty, full-time/part-time employment at the clinic, and certification as an infectious disease specialist. The questionnaire then presented three patient case scenarios, and respondents were asked to select answers on their testing and treatment strategies for each scenario. Scenarios 1, 2, and 3 were indicative of suspected aspiration pneumonia, suspected pyelonephritis, and suspected neoplastic fever, respectively. The questionnaire also included a follow-up scenario and question for Scenario 3.

Questions: For each scenario, respondents were asked about their testing and treatment strategies. Questions on testing included whether the respondents would obtain past bacterial culture results from the previous physicians, and which bacterial culture tests they would perform. Questions on treatments included whether they would initiate oral or parenteral antibiotic therapy, whether they would observe the patient without initiating antibiotic therapy, or whether they would refer the patient to a hospital. To detect differences in strategies according to medical and long-term care resource availability, respondents answered these questions for two different situations: own-home care (if the patient was living in his/her personal home) and residential care (if the patient was living at a residential care facility). If respondents chose to administer antibiotics, they were asked to specify the antibiotic type(s) that they would select for oral and parenteral administration. In the follow-up scenario for Scenario 3, we asked the duration of antibiotic administration after the patient's fever subsided. Detailed questions are shown in Supplementary Table S1 (https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=56).

Analysis: The proportions of the various responses were compared. Due to the small sample size, the comparison only involved descriptive analyses without statistical inference.

Ethical considerations: The study was approved by the institutional review boards of the National Center for Global Health and Medicine (Approval Number: NCGM-G-002518-00) and Yushoukai Medical Corporation (Approval Number: 001).

Physician practices in home care settings for aspiration pneumonia, pyelonephritis, and neoplastic fever

The questionnaire was sent to 36 physicians, of which 25 responded (response rate: 69.4%). The median duration since graduation was 14 years (interquartile range: 13-17 years). Among the respondents, 16 (64.0%) were internists, 7 (28.0%) were surgeons, 3 (12.0%) were anesthesiologists, and 1 (4.0%) did not respond. Physicians employed full-time at the clinics accounted for 80% of the respondents, and only one respondent (4.0%) was a certified infectious disease specialist.

The responses for the selected tests in each scenario are shown in Table 1. The proportions of respondents who would obtain past bacterial culture results from previous physicians were 64.0% for own-home care and 60.0% for residential care in Scenario 1 (aspiration pneumonia), 44.0% for both own-home care and residential care in Scenario 2 (pyelonephritis), and 44.0% for both own-home care and residential care in Scenario 3 (neoplastic fever). The proportions of respondents who

Table 2. Selected treatments in each scenario (*n* = 25)

Selected treatments	Own-home care	Residential care
Scenario 1 (Suspected aspiration pneumonia)		
Observe without initiating antibiotic therapy	2 (8.0)	3 (12.0)
Initiate oral antibiotic therapy	15 (60.0)	12 (48.0)
Initiate parenteral antibiotic therapy	8 (32.0)	10 (40.0)
Refer the patient to a hospital	0 (0.0)	0 (0.0)
Scenario 2 (Suspected pyelonephritis)		
Observe without initiating antibiotic therapy	3 (12.0)	3 (12.0)
Initiate oral antibiotic therapy	8 (32.0)	8 (32.0)
Initiate parenteral antibiotic therapy	14 (56.0)	14 (56.0)
Refer the patient to a hospital	0 (0.0)	0 (0.0)
Scenario 3 (Suspected neoplastic fever)		
Observe without initiating antibiotic therapy	20 (80.0)	20 (80.0)
Initiate oral antibiotic therapy	2 (8.0)	2 (8.0)
Initiate parenteral antibiotic therapy	3 (12.0)	3 (12.0)
Refer the patient to a hospital	0 (0.0)	0 (0.0)

Values are presented as *n* (%).Own-home care refers to care provided to patients living at home, whereas residential care refers to care provided to patients living at a residential facility.

would obtain a sputum culture in Scenario 1 were 76.0% for own-home care and 80.0% for residential care, and the proportions of respondents who would obtain a urine culture in Scenario 2 were 76.0% for both own-home care and residential care. In contrast, the proportions of respondents who would obtain a sputum or urine culture in Scenario 3 were much lower at 36.0% and 24.0%, respectively (both own-home care and residential care). Similarly, the proportions of respondents who would obtain blood cultures for Scenarios 1, 2, and 3 were low at 32.0%, 40.0%, and 28.0%, respectively (both own-home care and residential care).

The responses for the selected treatments in each scenario are shown in Table 2. The proportions of respondents who would observe the patients without initiating antibiotic therapy were 8.0% for own-home care and 12.0% for residential care in Scenario 1, 12.0% for both own-home care and residential care in Scenario 2, and 80.0% for both own-home care and residential care in Scenario 3. In Scenario 1, a higher proportion of respondents chose to initiate oral antibiotic therapy than parenteral antibiotic therapy (60.0% *vs*. 32.0% in own-home care and 48.0% *vs*. 40.0% in residential care); however, this pattern was reversed in Scenario 2 (32.0% *vs*. 56.0% for both own-home care and residential care). None of the respondents chose to refer the patient to a hospital in any scenario. For the follow-up question in Scenario 3, 44.0% of respondents chose to discontinue the prescribed antibiotics, whereas 52.0% of respondents would continue antibiotic therapy for a total of one week. The remaining 4.0% did not respond to this question. None of the respondents chose to continue antibiotic therapy for two weeks or to change antibiotics.

Responses for the selected antibiotics in each scenario are shown in Supplementary Table S2 (https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=56). In all scenarios, there was a general trend to select cephalosporins for parenteral antibiotics and quinolones for oral antibiotics.

This questionnaire study examined infectious disease management practices by home care physicians in Japan. The analysis shed light on the respondents' choices for testing and treatment in three scenarios that described cases of suspected aspiration pneumonia, pyelonephritis, and neoplastic fever in older patients with terminal cancer.

The study's major findings are as follows: first, only approximately 60% and 40% of respondents chose to obtain past bacterial culture results for Scenarios 1 and 2, respectively. Since previous bacterial culture results can guide antibiotic selection (*7*), obtaining information about previous test results when a patient transitions from hospital to home care is a prudent practice. The findings showed that preparing cultures from infected organs before administering antibiotics is relatively common, even in home-care settings. However, obtaining blood cultures is not a common practice. Occasionally, blood cultures detect the causal microorganisms of bacteremia and provide useful microbiological information to the doctors. However, guidelines of infectious diseases evaluation in long-term care facilities (LTCF) developed by Infectious Diseases Society of America (IDSA) suggests limited use of blood cultures due to the difficulty of bacteremia treatment in home-care settings (*8*). Due to the numerous limitations of consultation time, equipment, and treatment availability in home care, infectious disease management is not always required to be performed with the same level of detail and regularity as that in hospital care.

The respondents tended to select oral antibiotics for Scenario 1 and parenteral antibiotics for Scenario 2. Oral antibiotics can be used to effectively treat complicated pyelonephritis (*9*), and Japanese guidelines recommend oral antibiotics as first-line therapy for mild-to-moderate infections (*10*). Recommendations of oral antibiotics toward complicated pyelonephritis could be encouraged

more to avoid unnecessary parenteral drug administration and reduce the workload of medical staff and caregivers. Next, 80% of respondents chose to observe the patient without initiating antibiotic therapy for Scenario 3. This finding indicates that the majority of our respondents prioritized the diagnostic process over immediately starting antibiotic therapy. For the follow-up question in Scenario 3, approximately half of the respondents chose to discontinue the prescribed antibiotics, whereas the other half chose to continue therapy for one week. The early discontinuation of antibiotics for neoplastic fever cases represents a more judicious approach that prevents antibiotic resistance.

In the selection of antibiotic types, we observed a general trend toward cephalosporins for parenteral antibiotics and quinolones for oral antibiotics, regardless of scenario or own-home/residential care. We posit that this was influenced by the availability of antibiotics that only require a single daily dose (ceftriaxone for parenteral administration and levofloxacin for oral administration), which makes it easy to prescribe in home care settings. However, guidelines do not recommend these antibiotics for aspiration pneumonia (*11*), which occurs relatively frequently at home, due to their ineffectiveness against anaerobic bacteria.

The findings indicate the complexity of testing and treatment during infectious disease management. In order to standardize the quality and testing and treatment practices for infectious diseases in home-care settings, formulating guidelines of best practices for infectious disease management in home care should be considered. Currently, many guidelines regarding infection control and prevention have been developed for home-care settings because of the COVID-19 pandemic (*12,13*). However, guidelines regarding management of infectious diseases are otherwise scarce. IDSA guidelines for the management of infectious diseases in LTCF, updated in 2008, are well designed and provide useful information to doctors about home-care management of infectious diseases (*8*). However, these guidelines do not address treatment of diseases, and only target LTCF and not nursing home or patient's own home. Furthermore, American and Japanese home-care settings are different, potentially requiring domestic guidelines in Japan.

This study has several limitations. First, the sample may be vulnerable to selection bias because the respondents were all affiliated with the same medical corporation, and our findings may not be representative of all home care physicians in Japan. Second, the study used a questionnaire, and is therefore susceptible to response bias where respondents tend to select socially desirable answers. Third, although our questionnaire provided detailed information on the patient's characteristics in each scenario, it did not specify the differences between own-home care and residential care. For example, differences in the availability of caregivers around a patient can influence a physician's decisions.

In conclusion, our questionnaire-based analysis explored the current testing and treatment strategies for infectious diseases in home care settings. Future studies should examine the formulation of guidelines to standardize home care and improve antibiotic use in this field.

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References

1. Statistics Bureau of Japan. Statistical Handbook of Japan 2020. *https://www.stat.go.jp/english/data/handbook/c0117.html* (accessed September 8, 2022).
2. Ministry of Health, Labour and Welfare of Japan. Integrated community care system. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hukushi_kaigo/kaigo_koureisha/chiiki-houkatsu/ (accessed September 8, 2022). (in Japanese)
3. Yokobayashi K, Matsushima M, Watanabe T, Fujinuma Y, Tazuma S. Prospective cohort study of fever incidence and risk in elderly persons living at home. BMJ Open. 2014; 4: e004998.
4. Yokobayashi K, Matsushima M, Fujinuma Y, Tazuma S. Retrospective cohort study of the incidence and risk of fever in elderly people living at home: A pragmatic aspect of home medical management in Japan. Geriatr Gerontol Int. 2013; 13:887-893.
5. Ministerial Meeting on Measures on Emerging Infectious Diseases. National Action Plan on Antimicrobial Resistance (AMR) 2016-2020. *https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf* (accessed September 8, 2022).
6. Takayama Y. Concept of infection control in home care – preparing for promotion of regional comprehensive care system. Japanese Journal of Infection Prevention and Control. 2019; 34:242-245. (in Japanese)
7. Popoola VO, Carroll KC, Ross T, Reich NG, Perl TM, Milstone AM. Impact of colonization pressure and strain type on methicillin-resistant Staphylococcus aureus transmission in children. Clin Infect Dis 2013; 57:1458-1460.
8. High KP, Bradley SF, Gravenstein S, Mehr DR, Quagliarello VJ, Richards C, Yoshikawa TT; Infectious Diseases Society of America. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. J Am Geriatr Soc 2009; 57:375-394.
9. Mombelli G, Pezzoli R, Pinoja-Lutz G, Monotti R, Marone C, Franciolli M. Oral *vs* intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. Arch Intern Med. 1999; 159:53-58.
10. Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy. Urinary tract infections. In: The JAID/JSC Guide to Clinical Management of Infectious

Diseases 2019. Life Science Publishing Co., Ltd., Tokyo, Japan, 2019: pp. 202-219. (in Japanese)
11. Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy. Respiratory tract infections. In: The JAID/JSC Guide to Clinical Management of Infectious Diseases 2019. Life Science Publishing Co., Ltd., Tokyo, Japan, 2019: pp. 85-159. (in Japanese)
12. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations to prevent SARS-CoV-2 spread in nursing homes. *https://cdn.ymaws.com/www.leadingageflorida.org/resource/resmgr/covid-19/2021/05/Interim_Infection_Prevention.pdf* (accessed September 8, 2022)
13. World Health Organization. Infection prevention and control guidance for long-term care facilities in the context of COVID-19. *https://apps.who.int/iris/bitstream/handle/10665/331508/WHO-2019-nCoV-IPC_long_term_care-2020.1-eng.pdf* (accessed September 8, 2022)

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A physician-nurse partnership *via* online healthcare platforms protects infertile women from anxiety and depression: A multi-center prospective study from Shanghai, China

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Abstract: Effective health interventions are a priority for future infertility research, and effective interventions in patient-centered care are still needed. A multi-center prospective study was conducted in order to investigate the effects of a physician-nurse partnership (patients receive guidance and health education *via* online healthcare platforms) on depression and anxiety disorders in infertile women. The women were randomly assigned to a physician-nurse partnership group (n = 90) or a routine treatment group (n = 90). The primary endpoints were self-rating anxiety scale and self-rating depression scale scores. This study also examined the waiting time as an outpatient and the frequency of using online medical platforms. Compared to the routine treatment group, scores on the self-rating anxiety scale (48.4) and the self-rating depression scale (48.0) were significantly lower in the physician-nurse partnership group (p = 0.004, p = 0.001). Moreover, the mean waiting time (3.4) was shorter and online platforms (6.1) were used more frequently in the physician-nurse partnership group than in the routine treatment group (p < 0.001, p < 0.001). These data suggest that a physician-nurse partnership could reduce patients' anxiety, depression, and their waiting time as an outpatient.

***Keywords*:** physician-nurse partnership, infertility, depression, anxiety, waiting time

Introduction

A woman is considered infertile when she fails to conceive after at least 12 uninterrupted months of unprotected sexual activity (*1*). Research has increasingly indicated that the most common causes of infertility, such as polycystic ovary syndrome, endometriosis, fibroids, and diminished ovarian reserve, may lead to chronic morbidity later in life (*2*). These couples have been burdened with a heavy financial and mental toll, as well as a major expenditure of time spent on care, posing various challenges for the healthcare system (*3*).

Anxiety and depression are highly prevalent in infertile patients and their partners (*4*), and their distress could adversely impact themselves, their family, and their healthcare team. The specific impacts of anxiety and depression on infertile women are: *i*) symptoms of anxiety or depression are often characterized as the most upsetting experience in their lives (*5*); *ii*) patients suffering from psychological distress are more likely to lose confidence and terminate treatment; *iii*) the prevalence of psychological distress may lead to lower pregnancy rates; and *iv*) they pose additional challenges for the healthcare team. As the demands on the healthcare system continue to grow, delayed access to treatment, increased healthcare costs, and poor clinical outcomes lead to patient dissatisfaction, misunderstanding, and anxiety (*6*). '

The goal of infertility treatment is to maximize the chances of infertile women becoming mothers, and much needs to be done (*7*). A physician-nurse partnership is characterized by open communication, respect, and trust, as well as shared decision-making (*8*). An effective physician-nurse partnership can improve the quality of care, patient outcomes, and satisfaction among nurses and physicians and also decrease the cost of healthcare (*9*). Recent advances in information technology, such as the Internet, have revolutionized access to health information. Patients can use the

Internet to access a wide range of information and obtain support. Use of online systems also minimized face-to-face support during the COVID-19 pandemic (*10*).

The current study was designed as a multi-center prospective study to assess if a physician-nurse partnership benefits infertile patients who opted to receive assisted reproductive treatment. Scores on a self-rating anxiety scale (SAS) and a self-rating depression scale (SDS) were used as the primary endpoint to assess the patients' anxiety and depression. In addition, data on time spent as an outpatient and the frequency of using online platforms were collected in accordance with the hypothesis that a physician-nurse partnership could reduce patients' anxiety and depression and be associated with a favorable outcome.

Study design and data collection

Study design

This study was a multi-center prospective study conducted from January 2018 to December 2021 at the Obstetrics and Gynecology Hospital of Fudan University and Shanghai Ninth People's Hospital. Informed consent was obtained, and all patients agreed to participate in this study. The study subjects were married females (24-40 years of age) who failed to conceive regularly for more than one year during unprotected sexual intercourse and who opted to receive assisted reproductive treatment. Women who violated the protocol of this study or who refused to continue treatment were excluded. Male infertility was excluded from this study. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University (2019-57).

Subjects

One hundred and eighty patients who had provided informed consent in writing were randomly assigned to a physician-nurse partnership group (n = 90) or a routine treatment group (n = 90) between January 1, 2018, and December 31, 2021. All of the subjects (180, 100%) completed the study, and no patients were excluded from the efficacy analysis. Patients' mean age, body mass index (BMI), duration of infertility, history of smoking, obstetric history, and one's reason for opting to receive assisted reproductive treatment were noted (Table 1).

Procedures

In the physician-nurse partnership group, patients received guidance and health education *via* online healthcare platforms (including the Haodf app, WeChat app, or Xingren doctor app). As part of the physician-nurse partnership: *i*) patients who opt to receive assisted reproductive treatment are required to register with at least one of the online healthcare apps and to upload their medical records, *ii*) a nurse creates medical records for the patient, *iii*) a physician makes an appointment with the patient after reviewing records uploaded to the online platform and the physician then conducts a further examination, he or she makes a diagnosis, and he or she prescribes medication, *iv*) the physician conducts an in-person assessment of follicular development *via* transvaginal ultrasonography in which the nurse participates, and *v*) the physician and nurse answer patients' questions weekly on the platform and provide education about common problems to enhance

Table 1. Baseline characteristics of infertile patients

Variables	Total (n = 180)	Routine treatment group (n = 90)	Physician-nurse partnership group (n = 90)	p
Age, years, mean (SD)	33.0 (4.2)	32.8 (4.3)	33.0 (4.0)	0.695
BMI, kg/m^2, mean (SD)	21.6 (2.4)	21.7 (2.4)	21.6 (2.5)	0.781
Duration of infertility, years, mean (SD)	2.8 (1.8)	2.7 (2.0)	3.0 (1.5)	0.198
History of smoking, n (%)	85 (47.2)	52 (57.8)	49 (54.4)	0.652
Prior pregnancy outcomes, n (%)	-	-	-	-
Full-term pregnancy	13 (7.2)	4 (4.4)	9 (10.0)	0.150
Preterm pregnancy	5 (2.8)	3 (3.3)	2 (2.2)	0.650
Biochemical pregnancy	20 (11.11)	13 (14.4)	7 (7.8)	0.155
Spontaneous abortion	27 (15.0)	16 (17.8)	11 (12.2)	0.297
No pregnancy	115 (63.8)	54 (60)	61 (67.7)	0.277
Reason for opting to receive assisted reproductive treatment, n (%)	-	-	-	-
Diminished ovarian reserve	37 (20.5)	18 (20.0)	19 (21.1)	0.854
Endometriosis	14 (7.8)	8 (8.9)	6 (6.7)	0.310
Polycystic ovary syndrome	14 (7.8)	5 (5.5)	9 (10.0)	1.239
Uterine leiomyoma	31 (17.2)	15 (16.7)	16 (17.8)	0.844
Unexplained infertility	84 (46.7)	44 (48.9)	40 (44.4)	0.357

BMI: body mass index.

Table 2. Comparison of anxiety and depression assessments, the waiting time as an outpatient, and the frequency of using online platforms

Variables	Total (n = 180)			Routine treatment group (n = 90)			Physician-nurse partnership group (n = 90)			p
	Before	After	p	Before	After	p	Before	After	p	
Anxiety and depression assessments										
SAS score[†]	54.1 (6.7)	50.6 (4.6)	< 0.001	54.0 (6.4)	52.7 (4.3)	0.307	54.1 (7.0)	48.4 (4.0)	< 0.001	0.004
SDS score[†]	54.9 (7.2)	50.8 (4.7)	< 0.001	54.9 (7.2)	53.7 (3.0)	0.047	54.8 (7.1)	48.0 (4.3)	< 0.001	0.001
The waiting time as an outpatient										
Waiting time	-	4.0 (1.1)	-	-	4.6 (1.1)	-	-	3.4 (0.9)	-	< 0.001
The frequency of using online platforms										
Times	-	4.2 (2.0)	-	-	2.5 (0.7)	-	-	6.1 (0.9)	-	< 0.001

Data are expressed as the mean (SD). SAS: self-rating anxiety scale; SDS: self-rating depression scale. [†]Scores range from 25 to 100, with higher scores indicating greater severity.

communication between patients and the physician and nurse.

In the routine treatment group, patients seek to receive treatment conventionally: *i*) a patient who opts to receive assisted reproductive treatment makes an appointment offline or online, *ii*) a nurse creates medical records for the patient, *iii*) a physician conducts a further examination, he or she makes a diagnosis, and he or she prescribes medication, *iv*) the physician conducts an in-person assessment of follicular development *via* transvaginal ultrasonography, and *v*) the patients is verbally instructed during the process.

Outcome measures

As per the study schedule, effectiveness outcomes were evaluated after two weeks. The primary outcomes were the SAS and SDS scores, which were used to assess anxiety and depression (*11*). Both the SAS and SDS have 20 items, each of which was scored on a scale of 1-4 points. The SAS and SDS scores are 1.25 times the total raw scores. The overall severity is assessed on a scale of 25 to 100, where higher scores indicate greater severity. Secondary outcomes were the waiting time as an outpatient and the frequency of using online platforms. All adverse events were recorded during the study. With the nurse's help, all of the patients completed visits in person or by telephone.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Statistical analyses were performed using the software SPSS 23.0. Differences between the two groups were compared using the Mann-Whitney *U* test. A paired *t*-test was used to compare the results in each group to the baseline indicators, including age, BMI, and duration of infertility. The chi-square test was used to compare the history of smoking. $P < 0.05$ was considered statistically significant.

Creation of a physician-nurse partnership *via* online healthcare platforms for infertile women

A physician-nurse partnership decreased anxiety and depression scores

There is increasing evidence that depression and anxiety are highly prevalent among infertile women (*12*). Thus, more attention needs to be paid to them and they need to be helped to overcome their psychological problems. Communication is essential in relationships and is highly correlated with better patient adherence to medical care. Patient-nurse, patient-physician, and physician-nurse communications are essential parts of the physician-nurse partnership and significantly impact patient outcomes (*13*). Since communication skills are one of the core requirements of doctors' and nurses' competency, practical strategies are highly recommended (*14*). Here, an effective physician-nurse partnership was put into practice and communication among patients, physicians, and nurses was enhanced, providing patients with a full understanding of their physical and mental condition. Results indicated that SAS and SDS scores for the physician-nurse partnership group decreased significantly compared to scores for the routine treatment group (Table 2), indicating that the physician-nurse partnership alleviated anxiety and depression in infertile patients.

A physician-nurse partnership reduced the waiting time as an outpatient and increased the frequency of using online platforms

Waiting time is a notable phenomenon in publicly funded healthcare systems (*15*). The process from registration, waiting, examination, and receiving a diagnosis to received medication usually takes several hours. Fertility is very time-sensitive because one of the most significant factors affecting the success of assisted reproductive treatment is a female's age. Time

spent waiting for treatment is detrimental for these patients. Reducing the waiting time as an outpatient may reduce the time required for treatment. Approaches can be adopted by clinical services to reduce patients' waiting time (*16*). Online resources are commonly used by patients to understand illnesses better and to obtain advice from physicians, thus improving the patient-physician relationship (*17*). In the current study, online healthcare platforms, including the Haodf app, WeChat app, and Xingren doctor app, were accessible to patients, allowing patients to register with these platforms and to understand their care. Patients can consult with medical personnel *via* these online healthcare platforms. The waiting time for healthcare was reduced, and patients chose to use the online healthcare platforms once they were informed of their benefits. The platforms helped to provide regular feedback to patients, physicians, and nurses. Use of online platforms, such as medical applications (apps) or WeChat, was recommended to patients, and the frequency of their use of online platforms during the study was determined. Online platforms were used more often by the physician-nurse partnership group than by the routine treatment group (Table 2).

Effective health interventions are a priority for future infertility research, and effective interventions in patient-centered care are still needed (*18*). In conclusion, an effective physician-nurse partnership was put into practice, *via* online platforms, and this approach helped to alleviate patient anxiety and depression, reduce their waiting time, and make are more efficient. The sincere hope is that this physician-nurse partnership will be embraced and used as a beneficial intervention.

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References

1. Carson SA, Kallen AN. Diagnosis and management of infertility: A review. JAMA. 2021; 326:65-76.
2. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell. 2021; 184:2807-2824.
3. Kiesswetter M, Marsoner H, Luehwink A, Fistarol M, Mahlknecht A, Duschek S. Impairments in life satisfaction in infertility: Associations with perceived stress, affectivity, partnership quality, social support and the desire to have a child. Behav Med. 2020; 46:130-141.
4. Rooney KL, Domar AD. The relationship between stress and infertility. Dialogues Clin Neurosci. 2018; 20:41-47.
5. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ, Moran LJ. Depression, anxiety and perceived stress in women with and without PCOS: A community-based study. Psychol Med. 2019; 49:1510-1520.
6. McIntyre D, Chow CK. Waiting time as an indicator for health services under strain: A narrative review. Inquiry. 2020; 57:46958020910305.
7. Forsey J, Ng S, Rowland P, Freeman R, Li C, Woods NN. The basic science of patient-physician communication: A critical scoping review. Acad Med. 2021; 96:S109-S118.
8. Tan TC, Zhou H, Kelly M. Nurse-physician communication - An integrated review. J Clin Nurs. 2017; 26:3974-3989.
9. Hitawala A, Flores M, Alomari M, Kumar S, Padbidri V, Muthukuru S, Rahman S, Alomari A, Khazaaleh S, Gopalakrishna KV, Michael M. Improving physician-patient and physician-nurse communication and overall satisfaction rates: A quality improvement project. Cureus. 2020; 12:e7776.
10. Sumikawa Y, Yamamoto-Mitani N. Transitional care during COVID-19 pandemic in Japan: Calls for new strategies to integrate traditional approaches with information and communication technologies. Biosci Trends. 2021; 15:55-57.
11. Li G, Jiang Z, Kang X, Ma L, Han X, Fang M. Trajectories and predictors of anxiety and depression amongst infertile women during their first IVF/ICSI treatment cycle. J Psychosom Res. 2021; 142:110357.
12. Evans-Hoeker EA, Eisenberg E, Diamond MP, Legro RS, Alvero R, Coutifaris C, Casson PR, Christman GM, Hansen KR, Zhang H, Santoro N, Steiner AZ. Major depression, antidepressant use, and male and female fertility. Fertil Steril. 2018; 109:879-887.
13. Sabone M, Mazonde P, Cainelli F, Maitshoko M, Joseph R, Shayo J, Morris B, Muecke M, Wall BM, Hoke L, Peng L, Mooney-Doyle K, Ulrich CM. Everyday ethical challenges of nurse-physician collaboration. Nurs Ethics. 2020; 27:206-220.
14. Liu Y, Huang Y, Gao H, Cheng X. Communication skills training: Adapting to the trends and moving forward. Biosci Trends. 2017; 11:142-147.
15. Reichert A, Jacobs R. The impact of waiting time on patient outcomes: Evidence from early intervention in psychosis services in England. Health Econ. 2018;

27:1772-1787.
16. Walsh M, Horan MA, Wingfield M. Reduced waiting times and improved efficiency for couples accessing public, outpatient fertility clinics in the National Maternity Hospital, Dublin, Ireland. Fertil Steril. 2020; 114:e109-e110.
17. Tan SS, Goonawardene N. Internet health information seeking and the patient-physician relationship: A systematic review. J Med Internet Res. 2017; 19:e9.
18. Duffy JMN, Adamson GD, Benson E, *et al*. Top 10 priorities for future infertility research: An international consensus development study. Fertil Steril. 2021; 115:180-190.

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Efforts of a Psychiatric Liaison Team in a ward with patients with severe coronavirus disease 2019

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Abstract: The rapid increase in inpatients during the coronavirus disease 2019 (COVID-19) pandemic acutely increased the workload of physicians and nurses caring for severely ill patients. Moreover, family visits were restricted for infection control purposes, and family members were unable to be briefed regarding a patient's condition because they tested positive or they had been in close contact with an infectious patient, thus increasing the burden on the patient's family and the medical staff. Therefore, our psychiatric liaison team intervened by attending briefing sessions for family members and online patient visits while also conducting sessions to provide information about mental health and relaxation sessions for the hospital's nurses to reduce their burden as much as possible. These efforts provided mental support for the patients' families while also reducing the challenges of and the burden on medical staff. If the number of severely ill patients increases rapidly and the burden on patients' families and medical staff increases, then we hope that these efforts will help to provide better psychological support to both families and staff.

***Keywords*:** COVID-19, team medicine, psychiatric liaison team, family support, bereaved family care, online patient visits

More than 2 years has passed since the extensive spread of coronavirus disease 2019 (COVID-19), and several waves of the infection have come and gone. In particular, the fifth wave in Japan saw a rapid increase in the number of patients with COVID-19 nationwide (Figure 1) (*1*), which also led to an increase in patients with severe COVID-19 (hereinafter referred to as severely ill patients) hospitalized at the National Center for Global Health and Medicine (NCGM) as well as mortality (Figure 2). This led to a mounting physiological and psychological burden, causing anxiety for the staff treating and caring for those patients. Numerous studies in Japan and abroad have reported the mental health problems that healthcare professionals have faced during the COVID-19 pandemic (*2-5*). Moreover, the NCGM has been forced to restrict visits to inpatients since March 2020 for infection control purposes, further increasing the burden on the patients themselves and the medical staff that care for them.

This report discusses the Psychiatric Liaison Team's efforts in a ward for severely ill patients in which patients with severe COVID-19 were being treated and cared for during the fifth wave of the pandemic.

The Psychiatric Liaison Team is a team whose multidisciplinary staff, including physicians, nurses, pharmacists, and clinical psychologist, collaborate with physicians and nurses in charge of each department to bridge the gap between psychiatric care and physical care and to provide more comprehensive medical care to inpatients. The activities of the Team are expected to increase the effectiveness of medical care (*6*). The NCGM's Psychiatric Liaison Team (hereinafter referred to as "the Team") consists of individuals from multiple professions, namely psychiatrists, a certified nurse specialist in psychiatric mental health nursing, and a psychotherapist. Capitalizing on their expertise, they provide team medical care to inpatients and their families who find themselves in complicated social and psychological states.

Circumstances for severely ill patients and their families

The impact of the ban on visitation was greater than expected for severely ill patients and their families and the medical staff in the ward in question. Patients' families experienced various hardships and internal conflicts, such as not knowing the patient's status and being unable to touch the patient, much like the severely ill patients themselves. Nurses working on the ward had to spend many hours responding to phone calls from patients' families who were barred from visitation (at

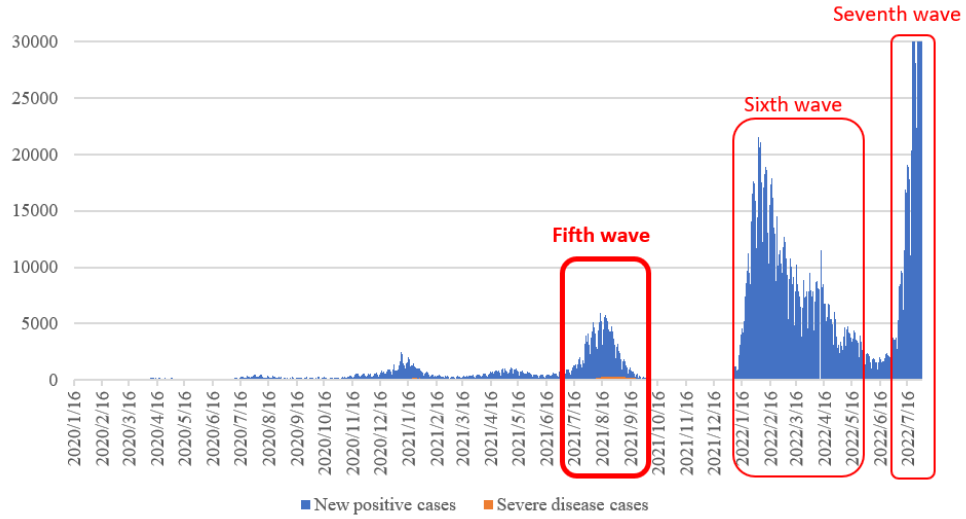

Figure 1. New positive cases/cases of severe disease in Tokyo, Japan. Data from the Ministry of Health, Labor, and Welfare.

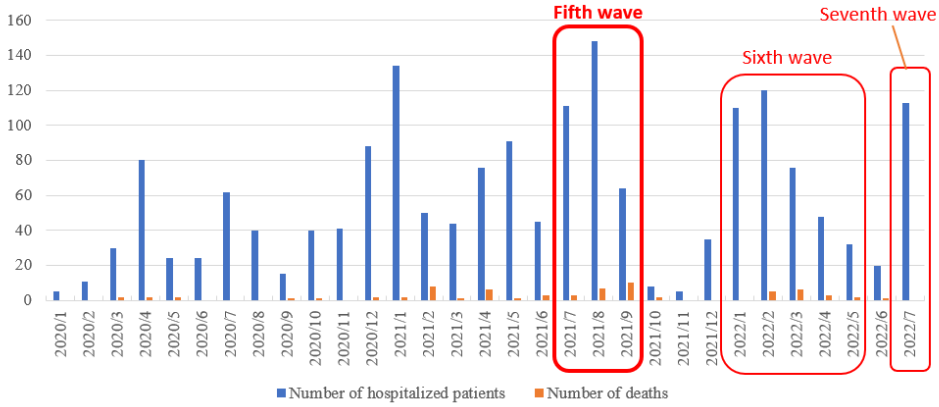

Figure 2. Number of hospitalizations/deaths due to COVID-19 in this hospital from January 2020 to July 2022.

times, the families would express demands, requests, anxiety, and anger), which sometimes interfered with other work.

Doctors and nurses who treat and care for severely ill patients who require advanced medical care have also been under heavy stress. When briefing families about patients' conditions, doctors often have to convey the difficult details of the patient's condition, which would normally require careful family support. However, adequate family support was not provided due to the heavy workload of nurses in charge of the site.

Moreover, severely ill patients with cluster infections in the family had family members who had been instructed to stay at home or who were admitted to other hospitals, which prevented some families from visiting the NCGM. In such circumstances, even serious details about a patient's condition had to be explained over the telephone, which meant that hospital staff could not correctly ascertain the family's response after the briefing. In one case, the ward staff could not intervene even though the family was grieving profoundly and they had trouble accepting the situation. In August 2021, the ward's Head Nurse and a department doctor provided the Team with information about these situations.

What was expected of the Team

Soon after the briefing session by the ward's Head Nurse and a department doctor, the Team's psychiatric nursing specialist and psychotherapist solicited opinions about the Team's role. They confirmed that the following was needed from the Team: *i*) for a member of the liaison team to be in attendance to provide psychological support to the patients' families during a briefing session, which is expected to induce profound grief and shock in patients' families; *ii*) to follow-up with the patients' families about the patient's condition after the briefing session (to continue to meet with and provide psychological support to the patients' families); *iii*) to arrange online visits by families (from a location outside the hospital, such as at home) because some could not visit the hospital; and 4) to provide mental health

support to the nursing team working in the ward for severely ill patients.

What the Team has done

The following support was provided based on the ward's needs: *i*) patient family support: the Team's psychiatric nursing specialist or psychotherapist oversaw the briefing sessions on the patient's condition and online visits by the patient's family. They provided support so that the family could readily communicate with doctors and nurses, ask questions, and understand the patient's current situation. Through interviews with the families, they evaluated and confirmed the physical condition and psychological state of the family and also provided self-care education (sleep hygiene guidance, ideas about what to eat, and relaxation breathing); *ii*) bereaved family care: for the family members of patients who died of COVID-19, the Team arranged a setting in which the Team could continue to interview the family if they so wished, and they informed the family members to that effect; *iii*) made arrangements for online visits: the Team consulted with the department in charge at the hospital based on the Team's experience with prior online visits to see if online visits could be made from the outside (outside the hospital, such as from the patient's home), but external online visits were not possible; and *iv*) mental health support for the ward-based nursing team: the psychiatric nurse of the Team and clinical psychologist in the staff consultation department of the NCGM conducted mental health briefing sessions and relaxation sessions for the nursing team on the ward.

Effects of the Team's involvement

There were nine cases in which a member of the Team oversaw briefing sessions on the patient's condition and online visits by the patient's family as a form of family support. Patients' families had many positive things to say about the briefing sessions and online visits, such as "I was relieved to see my loved one's actual state on the iPad screen. Being able to convey my feelings to my loved one was nice" and "I am very thankful to the doctors and nurses who are doing their best." The bereaved families of patients who died of COVID-19 were informed that the Team can continue providing bereavement care, but no family members have requested it so far.

Changes in the ward staff were also noted; the doctors of the ward said that "the Team helped to reduce the burden of the briefing sessions on the patient's condition and providing family support" and "this provides us with a new system to deal with a rapid increase in COVID-19 infections and hospital admissions going forward." The Team's involvement affected the patients' families and it provided support to on-site staff.

Next steps for the Team

The Team has not been asked to care for a bereaved family thus far, but a study has reported that the need for bereaved family care is increasing due to the COVID-19 pandemic (*7*), and the creation of a system for bereaved family care will need to be considered in the future (providing information to bereaved families and greater access to bereaved family care).

Online visits both connect patients with their families and also connect patients' families with healthcare professionals. Patients' families need to be given safe places and ways to watch over their ill family member so that they are better prepared to accept the patient's death, and bereaved families need to receive specialized support even after the patient's death (*8*). These observations suggest that online visits that allow family members to safely see the patient should be made more accessible. At the NCGM, however, this cannot be implemented yet, despite family requests for online visits from the outside (access outside the hospital, such as at the family's home). The issues raised in conjunction with this lack of implementation include the inability of hospital staff to help the patient and family members understand how to operate the devices and security problems for the NCGM. These issues need to be addressed first.

The burden on the families of severely ill patients and the medical staff that care for these patients was greater than expected, and the burden on families and medical staff is expected to increase as the number of severely ill patients increases and responses become prolonged as the infection continues to spread. If the number of infected or severely ill patients increases again, the Team would like to capitalized on its previous efforts and implement a wide range of approaches to help support patients, patients' families, and medical staff as well.

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References

1. Ministry of Health, Labour, and Welfare. Visualizing the data: Information on COVID-19 infections. *https://*

covid19.mhlw.go.jp/ (accessed August 25, 2022). (in Japanese)
2. Watanabe Y, Someya T. Feature Article - Suicide prevention measures during the COVID-19 pandemic and the mental health of healthcare workers. Japanese Journal of Public Health. 2021; 85:156-159. (in Japanese)
3. Hamouche S. COVID-19 and employees' mental health: Stressors, moderators and agenda for organizational actions. Emerald Open Research. 2020; 2:15.
4. Giorgi G, Lecca LI, Alessio F, Finstad GL, Bondanini G, Lulli LG, Arcangeli G, Mucci N. COVID-19-related mental health effects in the workplace: A narrative review. Int J Environ Res Public Health. 2020; 17:7857.
5. Sasaki N, Kawakami N. Mental health among workers in the COVID-19 pandemic: A review. Occupational Health Review. 2021; 34:17-50. (in Japanese)
6. Yoshimura Y, Kiriyama K, Fujiwara S. Current status and problems of the psychiatric liaison team. Japanese Journal of General Hospital Psychiatry. 2013; 25:2-8. (in Japanese)
7. Matsuda Y, Takebayashi Y, Nakajima S, Ito M. Managing grief of bereaved families during the COVID-19 pandemic in Japan. Front Psychiatry. 2021; 12:637237.
8. Firouzkouhi M, Alimohammadi N, Abdollahimohammad A, Bagheri G, Farzi J. Bereaved families views on the death of loved ones due to COVID 19: An integrative review. Omega (Westport). 2021:302228211038206.

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Stroke treatment during the COVID-19 pandemic

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Abstract: Studies have reported that COVID-19 is associated not only with pneumonia but also with cerebrovascular disease. Consequently, medical personnel involved in treating stroke in the emergency medicine setting have been placed in a situation that requires them to provide treatment while always remaining mindful of the possibility of COVID-19. Here, we describe the current state of stroke treatment during the COVID-19 pandemic. Four patients with stroke and concomitant COVID-19 were treated at our facility. We treated 3 patients with cerebral infarction and 1 patient with cerebral venous sinus thrombosis. All 3 patients with cerebral infarction had a poor outcome. This was attributed in part to the poor general condition of the patients due to concomitant COVID-19, as well as to the severity of the major artery occlusion and cerebral infarction. One patient with cerebral venous sinus thrombosis had a good outcome. Anticoagulant therapy was administered at our hospital and resulted in a stable clinical course. Our hospital has worked to establish an examination and treatment system that enables mechanical thrombectomy to be performed even during the COVID-19 pandemic. We devised a protocol showing the steps to be taken from initial treatment to admission to the cerebral angiography room. Our hospital was able to continue accepting requests for emergency admission thanks to the examination and treatment system we established. Up-to-date information should continue to be collected to create examination and treatment systems.

Keywords: COVID-19, stroke, cerebral infarction, cerebral venous sinus thrombosis, mechanical thrombectomy

Since it was first reported in December 2019, COVID-19 has spread throughout the world at an unprecedented speed. Studies have reported that COVID-19 is associated not only with pneumonia but also with cerebrovascular disease. Consequently, medical personnel involved in treating stroke in the emergency medicine setting have been placed in a situation that requires them to provide treatment while always remaining mindful of the possibility of COVID-19.

According to a survey by the Japan Stroke Society (*1*), an analysis of the current state of the emergency medicine system in Japan during the COVID-19 pandemic indicated that, of the 714 primary stroke centers, only 81.7% were accepting requests for emergency admission as they would under normal circumstances in December 2020. This figure was comparable to the situation when a state of emergency was declared (77.8% in May 2020). Eighteen-point-three percent of centers had some type of restriction on care, and 13 centers had to stop accepting requests for emergency admission.

Our hospital has worked to establish an examination and treatment system that enables mechanical thrombectomy to be performed even during the COVID-19 pandemic. After repeated consultations with the medical departments and units involved in stroke treatment, we devised a protocol showing the steps to be taken from initial treatment to admission to the cerebral angiography room (Figure 1). For emergency outpatient care, a rapid COVID-19 PCR test using a kit to detect nucleic acids of pathogenic microbes (FilmArray®) is performed immediately after the patient arrives to reduce the time required for COVID-19 evaluation. Because of the risk of exposure associated with tracheal intubation during treatment, patients for whom endovascular therapy is indicated are intubated in advance, during emergency outpatient care. If the patient definitively tests positive for COVID-19, the number of medical staff involved in the treatment is minimized, and the staff wear personal protective equipment. The steps to be taken from initial treatment to angiography room admission shown in the protocol were simulated using mannequins to establish measures to prevent infection and environmental contamination.

Between January 2020 and December 2021, mechanical thrombectomy was performed 54 times before the COVID-19 pandemic (2018 and 2019) and 40 times afterwards (2020 and 2021). Although our hospital was able to continue accepting requests for emergency admission thanks to the examination and treatment system we established, there was a decrease

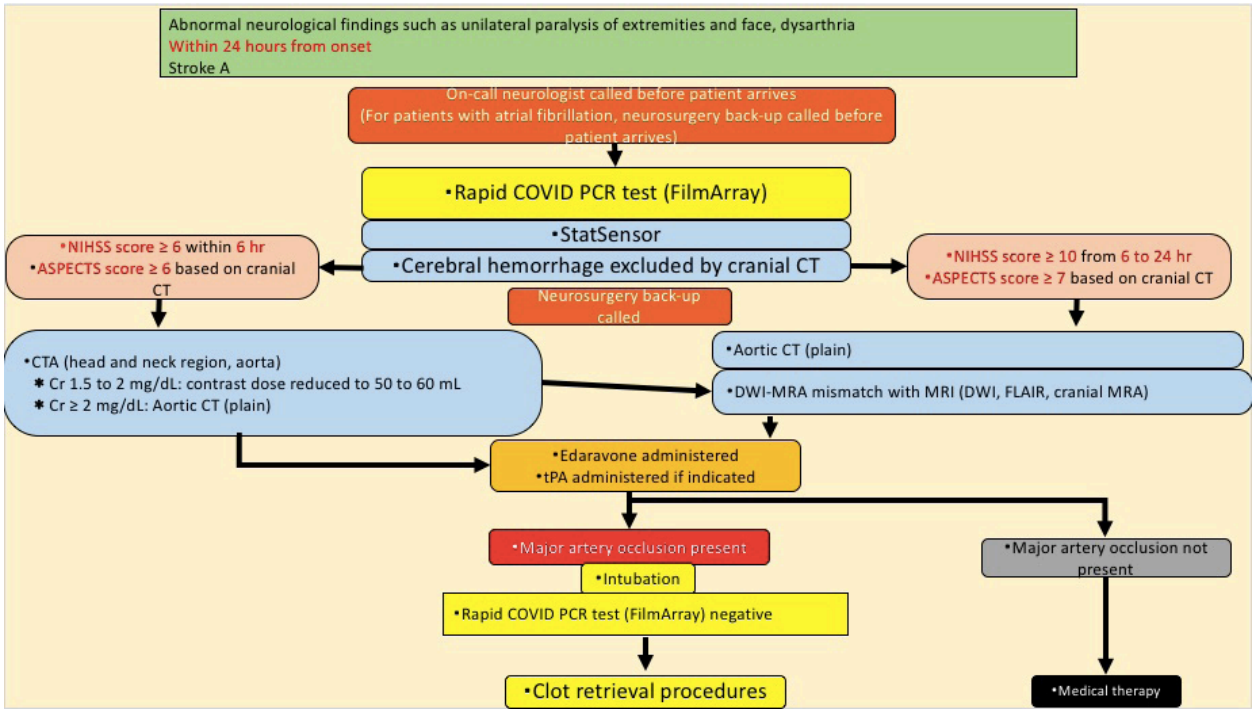

Figure 1. Protocol. This protocol shows the steps to be taken from initial treatment to admission to the cerebral angiography room.

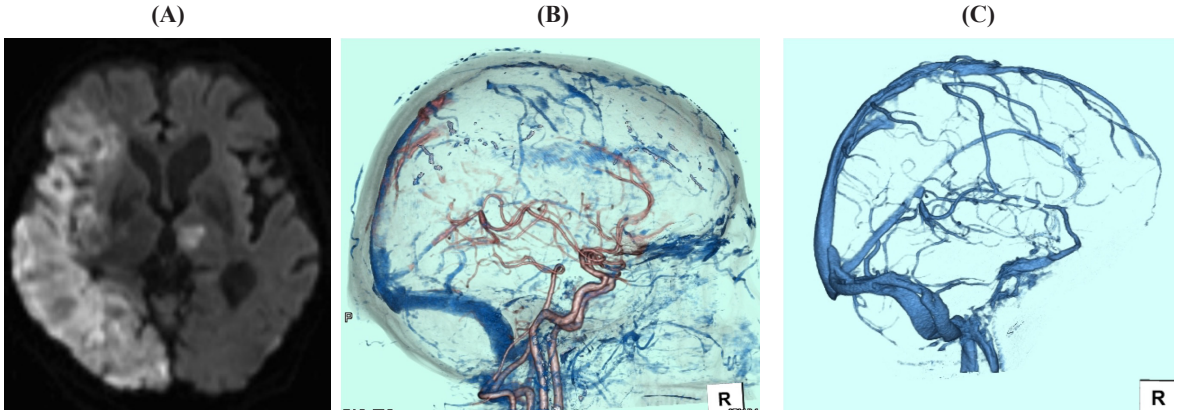

Figure 2. (A) A cranial MRI scan revealing acute infarcts from the right frontal lobe to the temporo-occipital lobe and in the left thalamus; **(B)** CTV revealed a deficit from the superior sagittal sinus to the right sigmoid sinus; **(C)** CTV 1 month later revealed alleviation of sinus thrombosis. MRI, magnetic resonance imaging; CTV, computed tomography venography.

in the number of times mechanical thrombectomy was performed. The mean time from hospital arrival to the start of treatment has increased from 93.2 minutes before the COVID-19 pandemic (2018 and 2019) to 105.6 minutes since its start (2020 and 2021). Moreover, the time from onset to hospital arrival has increased from 141 minutes to 150.4 minutes. Studies of stroke treatment during the COVID-19 pandemic have indicated that fewer patients were hospitalized for stroke and fewer clot removal procedures were performed during periods that COVID-19 increased. Changes in examination and treatment systems (the need to limit acceptance of non-COVID-19 patients as treatment of COVID-19 patients has increased) and in patient behavior (*e.g.*, patients with mild disease refraining from receiving treatment) have been discussed as possible causes (*2*).Moreover, the time from hospital arrival to the start of treatment has increased. This was attributed to additional steps taken before treatment, such as PCR testing and intubation.

We have not seen any patients with concomitant COVID-19 for whom mechanical thrombectomy was indicated, but four patients with stroke and concomitant COVID-19 were treated at our facility. Three of those patients had cerebral infarction. One was a 78-year-old male, one was a 55-year-old female, and the remaining one was an 80-year-old male who had major artery occlusion (Figure 2A). All 3 patients were treated conservatively but had a poor outcome. This was

attributed in part to the poor general condition of the patients due to concomitant COVID-19 as well as to the severity of major artery occlusion and cerebral infarction. We also treated one patient with cerebral venous sinus thrombosis, a 46-year-old man. Computed tomography venography (CTV) revealed a deficit from the superior sagittal sinus to the right sigmoid sinus, and the patient was diagnosed with cerebral venous sinus thrombosis (Figure 2B). Blood tests revealed an elevated D-dimer level (30.9). Anticoagulant therapy with heparin and warfarin was administered. The patient's clinical course was good, and follow-up CTV 1 month later revealed alleviation of sinus thrombosis (Figure 2C).

According to a review that summarized 26 studies of the relationship between COVID-19 and stroke from the first study to August 2020, the incidence of cerebral infarction in inpatients positive for COVID-19 was 1.5% (0.1% to 6.9%) (*3*). The fact that the incidence differed depending on the study suggested that imaging studies could not be adequately performed to prevent the spread of infection and that strokes may have been overlooked in patients on mechanical ventilation (*3*). Most of the strokes were cerebral infarctions, which accounted for more than 70% to 80% of the total. This was followed, in descending order, by cerebral hemorrhage (approximately 10% to 15%), cerebral sinus thrombosis (approximately 0.5% to 4%), and subarachnoid hemorrhage (*4*). Examination by type of cerebral infarction indicated that cerebral infarction with no identifiable cause (cryptogenic cerebral infarction) was the most common. This was followed, in descending order, by cardiogenic brain embolism, atherothrombotic cerebral infarction, and lacunar infarction (*4*). Multiple vascular areas were often affected, and many patients tended to have a concomitant intracerebral hemorrhage or major artery occlusion. Compared to non-stroke patients, those with concomitant stroke were older and more often had hypertension, diabetes mellitus, coronary artery disease, and severe COVID-19 (*4*).

Cerebral venous sinus thrombosis was reported in 39 patients in March 2021. The time of onset was most often within 8 days of diagnosis of COVID-19, which was the case in 67% of the patients, and the most common symptoms included headaches, convulsions, and stroke-like symptoms. As is the case for normal cerebral venous sinus thrombosis, anticoagulant therapy was the treatment most commonly administered (*5*). Anticoagulant therapy was also administered at our hospital and resulted in a stable clinical course.

The current study has described the current state of stroke treatment during the COVID-19 pandemic. Up-to-date information should continue to be collected to create examination and treatment systems.

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References

1. The Japan Stroke Society. Survey on the impact of COVID-19 on stroke emergency care - Statement based on the December 2020 Situation. *https://www.jsts.gr.jp/news/pdf/20210105_covid.pdf* (accessed march 23, 2022). (in Japanese)
2. Nogueira RG, Abdalhader M, Qureshi MM, *et al*. Global impact of COVID-19 on stroke care. Int J Stroke. 2021; 16:573-584.
3. Sagris D, Papanikolaou A, Kvernland A, Korompoki E, Frontera JA, Troxel AB, Gavriatopoulou M, Milionis H, Lip GYH, Michel P, Yaghi S, Ntaios G. COVID-19 and ischemic stroke. Eur J Neurol. 202; 28:3826-3836.
4. Kawano H. COVID-19 and stroke. Jpn J Thrombosis Hemostasis 2021; 32:723-725.
5. Ghosh R, Roy D, Mandal A, Pal SK, Chandra Swaika B, Naga D, Pandit A, Ray BK, Benito-León J. Cerebral venous thrombosis in COVID-19. Diabetes Metab Syndr. 2021; 15:1039-1045.

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LETTER

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How should support for hospital staff during health shocks be improved? A discussion from Japan's experience during the COVID-19 pandemic

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Abstract: Human resources for health are at the center of healthcare service delivery and play an important role in ensuring the resilience of health systems. Utilizing the results from a case study examining hospital resilience during COVID-19, this article draws on the experience of individual hospital staff during the first and second waves of the pandemic, briefly describes government responses to support human resources for health during the early stages of the pandemic, and argues the importance of constructive discussions about strategies to create an enabling work environment for healthcare providers, both clinical and non-clinical, during future health shocks.

***Keywords*:** human resources for health, health system resilience, enabling work environment

Since the COVID-19 pandemic commenced, human resources for health have been challenged in their roles as caregivers at the frontline of healthcare service delivery. We conducted a case study in Japan as part of a multi-country study investigating hospital resilience, and undertook an in-depth analysis at two hospitals to determine how the hospitals overcame the disruptions caused by COVID-19 in the early stage of the pandemic (*1*).

The case study found that, during the first two waves of the COVID-19 pandemic, there were insufficient clinical staff available to care for patients due to: a rapid increase in patient numbers; infection control measures taking more time than with usual patients; and hospital staff being required to undertake additional tasks on top of their usual work. To increase the number of clinical staff available to provide care to COVID-19 patients, hospitals: *i*) temporally recruited medical doctors from other hospitals, particularly to provide care to patients with severe COVID-19 symptoms at the beginning of the first wave; *ii*) redeployed clinical staff to departments caring for COVID-19 patients, and provided care using staff from multiple hospital departments (task-sharing between different departments); and *iii*) introduced task-shifting for administrative staff and nurses (*i.e.*, tasks usually undertaken by other professional groups were re-distributed to administrative staff and nurses), particularly after the suspension of non-clinical services and services delivered by external providers.

Throughout the first and second waves of the pandemic, the staff at healthcare facilities providing COVID-19-related services operated under significant pressure. The underlining causes of the stress experienced by healthcare facility staff included: heavy workloads and additional responsibilities; unfamiliar methods of providing care due to new and increased infection control measures; insufficient community understanding of COVID-19 and healthcare providers; fear of infection through work; and continuing pressure for individual healthcare providers to remain uninfected by COVID-19. In addition, at the onset of the pandemic, constantly changing information about the 'unknown' virus and lack of clear evidence for the response to the pandemic increased fear and confusion at the frontline of healthcare service delivery.

Support provided to human resources for health during the first and second waves of pandemic

In response to the increased workload, fear, and stress experienced by frontline healthcare providers due to COVID-19, many countries introduced additional support measures for health workers. The measures included: *i*) mental and well-being support, mainly through newly-established helplines or remote counselling sessions for healthcare workers; *ii*) financial compensation, often in the form of one-time bonuses or temporary salary increases paid to both individuals and

facilities to recognize the efforts of healthcare providers; and *iii*) practical support to enable health workers to keep working, including keeping schools open for the children of health workers when closed to other members of the public (*2,3*).

The policy responses for issues relating to human resources for health during the first and second waves of the COVID-19 pandemic in Japan are summarized in Table 1. The Japanese Government, through local governments, introduced one-off payments for individual healthcare providers and the health facility staff who directly provided services to COVID-19 patients, with payments ranging from JPY 50,000 to JPY 200,000, depending on the facility type (*4*). Subsidies were also provided to healthcare facilities to improve the working conditions, including salaries, of staff providing clinical services to COVID-19 patients (*5*). The Government provided financial support to health facilities offering in-facility nursery care for the children of staff and attempted to facilitate childcare options for healthcare providers during temporary school closures (*6,7*). In addition, the Government created a mechanism to contribute part of the premiums for private occupational injury insurance for healthcare professionals working at facilities providing care to COVID-19 patients (*8*). As Table 1 shows, the policy measures that were introduced to address issues associated with human resources for health in the early stages of the COVID-19 pandemic in Japan focused on financial payments and practical support.

Table 1. Policy responses to protect individual healthcare providers during the first and second waves of the COVID-19 pandemic in Japan

Date	Policy response	Objective	Beneficiary of response
Mar. 4, 2020	Securing places for the children of healthcare workers by using in-house childcare centers in response to the temporary closure of schools aimed to prevent novel coronavirus infection (request) (Ministry of Health, Labor, and Welfare (MHLW) administrative communication)	To enable health professionals with school age children to continue to work during temporary COVID-19 related closures of schools so that the healthcare system could continue to function.	Healthcare professionals
Mar. 4, 2020	Notes on the priority use of after-school childcare in response to temporary school closures that aim to prevent the spread of coronavirus (MHLW Administrative Communication)	To prioritize access to after-school childcare and healthcare services for children with parents working in the social sector during temporary closures of primary schools due to the COVID-19 pandemic.	Those working in social service sector, including medical and nursing care staff
Mar. 11, 2020	Emergency support for medical institutions accepting COVID-19 patients (including those delivering COVID-19-related services)	To support healthcare professionals working in health facilities that accepted COVID-19 patients, and to strengthen COVID-19 related service delivery.	Those involved in COVID-19 related services, including both clinical and non-clinical staff
Apr. 17, 2020	Response to the new coronavirus in daycare centers for children of healthcare workers and others (MHLW Administrative Communication)	To prepare for a reduction in the size of nursery schools or temporary closure of nursery schools and ensure that medical personnel are not forced to stay at home, take a leave of absence or leave their jobs due to a lack of places for children in childcare during the COVID-19 pandemic; and to ensure that there is no prejudice or discrimination against healthcare professionals and their children, such as refusal to care for the children of healthcare workers.	Healthcare professionals
Jun.16, 2020	Support grant/bonus for the novel coronavirus response workers	To provide a financial bonus for services provided by healthcare professionals and health facility staff, who were under considerable physical and mental strain as a result of their role in the COVID-19 pandemic. The medical personnel and staff working at the healthcare facilities that were assigned by local government to provide medical treatment for COVID-19 patients and those in direct contact with patients receive JPY 200,000 as a bonus payment (JPY 100,000 if there is no acceptance of COVID-19 cases at the health facility). Medical personnel and staff in other health facilities who had contact with COVID-19 patients receive JPY 50,000.	Medical personnel and staff working at medical facilities designated by local governments to provide medical care for COVID-19 patients and who had contact with COVID-19 patients Medical personnel and staff who work in non-COVID-19 treating health facilities and who had contact with COVID-19 patients
Dec. 10, 2020	Thorough handling of the response to the novel coronavirus in day-care centers for the children of health-care workers (MHLW Administrative Communication)	To address the misconception towards healthcare professionals and their children and avoid the case in which preschools refuse the attendance of children due to parental occupation/workplace.	Healthcare professionals and those working in the social sector
Apr. 1, 2021	Support for workers at the health facilities responding to novel coronavirus infection to join the workers' compensation insurance scheme and obtain additional worker compensation benefits	Government to subsidize insurance premiums for qualified healthcare professionals who work at healthcare facilities providing COVID-19 related services when joining a private insurance scheme that provides additional benefits in the event of COVID-19 infection.	Qualified healthcare professionals who work at healthcare facilities providing COVID-19 related services

Adequacy and effectiveness of the support for healthcare providers – points for future consideration

The supportive policy measures provided to the human resources for health during the first and second waves of the pandemic in Japan were often implemented as issues arose and the effectiveness of these measures has yet to be thoroughly evaluated (*2*). While a comprehensive assessment is required of both the support provided to human resources for health during the early stages of the pandemic and how supportive policy measures were actually implemented, the findings from the case study in Japan indicate the following should be considered to improve support for healthcare workers:

i) Equitable provision of financial support: while maintaining hospital operations during a pandemic occurs due to the collective efforts of all hospital staff, financial support was only given to the (mainly clinical) staff involved in the direct delivery of COVID-19 related services. To achieve equity, some hospitals rotated the staff delivering COVID-19 related services so that most clinical staff received financial compensation and benefits were not limited to small group.

ii) The impact of temporary salary increases: the provision of temporary salary increases to those involved in COVID-19-related healthcare services can produce unexpected effects (*9*). The incentive signal created by short-term salary increases should be carefully considered for future improvements in the provision of financial support during health shocks.

iii) Examination of gaps in understanding the types of support needed during health shocks: Although the measures to support human resources for health were developed in response to the unexpected COVID-19 pandemic, in Japan, in some areas, broader health system support was lacking, such as support for mental health. It is vital to identify the types of support that were valued by individual healthcare workers during the COVID-19 pandemic in order to adequately deliver healthcare services during future health crises.

Human resources for health are at the centre of healthcare service delivery and play an important role in ensuring the resilience of health systems (*10*). This letter article is based on an examination of the early stages of the COVID-19 pandemic in Japan. As the pandemic has continued to evolve since the study was undertaken, the challenges encountered by human resources for health have changed and it is imperative to continue to examine the support required for people at the frontline healthcare service delivery so the health system can function appropriately. Constructive examination of the effects of supportive measures on human resources for health during the COVID-19 pandemic, and identification of the types of support most valued during the COVID-19 experience will inform strategies to create enabling environments for healthcare providers, both clinical and non-clinical, in future health shocks.

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References

1. Ridde V, Gautier L, Dagenais C, et al. Learning from public health and hospital resilience to the SARS-CoV-2 pandemic: protocol for a multiple case study (Brazil, Canada, China, France, Japan, and Mali). Health Research Policy and Systems. 2021; 19:76.
2. Winkelmann J, Webb E, Williams GA, Hernández-Quevedo C, Maier CB, Panteli D. European countries' responses in ensuring sufficient physical infrastructure and workforce capacity during the first COVID-19 wave. Health Policy. 2022; 126:362-372.
3. Williams GA, Scarpetti G, Bezzina A, Vincenti K, Grech K, Kowalska-Bobko I, Sowada C, Furman M, Gałązka-Sobotka M, Maier CB. How are countries supporting their helath workers during COVID-19? Eurohealth. 2020; 58-62.
4. Ministry of Health Labour and Welfare. Support grant/ bonus for the novel coronavirus response workers. *https://www.mhlw.go.jp/content/10800000/000640500.pdf* (accessd July 20, 2022). (in Japanese)
5. Ministry of Health Labour and Welfare. Subsidy for emergency support project for medical institutions accepting COVID-19 patients]. *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou18/index_00015.html* (accessd July 20, 2022). (in Japanese)
6. Ministry of Health Labour and Welfare. Securing places for the children of healthcare workers by using in-house childcare centers in response to the temporary closure of schools aimed to prevent novel coronavirus infection (request) *https://www.pref.fukushima.lg.jp/uploaded/attachment/373631.pdf* (accessd July 2022). (in Japanese)
7. Ministry of Health Labour and Welfare. Notes on the priority use of after-school childcare in response to temporary school closures that aim to prevent the spread of coronavirus. *https://www.mhlw.go.jp/content/11920000/000604481.pdf* (accessd July 20, 2022). (in Japanese)
8. Ministry of Health Labour and Welfare. Support for workers at the health facilities responding to novel coronavirus infection to join the workers' compensation insurance scheme and obtain additional worker compensation benefits. *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000098580_00006.html* (accessd July 20, 2022). (in Japanese)
9. European Observatory on Health Systems and Policies, Sagan A, Webb E, Azzopardi-Muscat N, Mata Idl, McKee M, Figueras J (2021). Health systems resilience during COVID-19: Lessons for building back better. World Health Organization. Regional Office for Europe. *https://apps.who.int/iris/handle/10665/348493?locale-attribute=en&* (accessd July 20, 2022).
10. Thomas S, Sagan A, Larkin J, Cylus J, Figueras J, Karanikolos M. Strengthening health systems resilience:

Key concepts and strategies [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2020. *https://www.ncbi.nlm.nih.gov/books/NBK559803/* (accessd July 20, 2022).

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The development of SARS-CoV-2 PCR testing methods at a designated medical institution for specific infectious diseases in Japan

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Abstract: Due to the coronavirus disease 2019 (COVID-19) pandemic, we have been conducting polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at this facility since March 2020. In the early days, the PCR testing system had limited capabilities, so testing had to be conducted manually and only a few tests were conducted. Moreover, we lacked sufficient experience to conduct PCR testing manually, so we struggled with the manual work, which required intense concentration, and we felt pressured not to make mistakes such as allowing contamination. Since we introduced upgraded equipment, new methods, and additional staff for testing and we cooperated with the clinical technologist on the night shift in the Emergency Department, we are currently able to conduct urgent PCR testing on more than 2,000 specimens per month 24 hours a day. We will continue to meet new needs for COVID-19 treatment with the cooperation of other departments.

***Keywords*:** SARS-CoV-2, PCR testing

Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since February 2020, the Clinical Laboratory at our hospital (a designated medical institution for specific infectious diseases in Japan) has gradually enhanced its polymerase chain reaction (PCR) testing system for SARS-CoV-2 to meet the needs for COVID-19 treatment. Here, I would like to explain the development of our system and methods for SARS-CoV-2 PCR testing used at this hospital over the past two years.

Events related to the PCR testing system for SARS-CoV-2 over the past two years (Table 1)

In March 2020, the Clinical Laboratory introduced an in-hospital SARS-CoV-2 PCR testing system. In the early days, the testing system had limited capabilities, so testing had to be conducted manually and few tests were conducted. Since we introduced upgrading equipment, modified methods, and additional staff for testing, the number of tests gradually increased. In July, reagents for automated equipment were supplied. This allowed us to increase the number of tests. In August, urgent PCR testing started with the cooperation of the clinical technologist on the night shift in the Emergency Department. We conducted around-the-clock testing for patients who required emergency hospitalization or surgery.

In January 2021, we started PCR testing for recipients of full medical checkups. In March, we started PCR testing to detect the N501Y and E484K mutation of the SARS-CoV-2 spike protein in new patients with COVID-19. In June, we further added PCR testing to detect the L452R mutation of the SARS-CoV-2 spike protein. In July, we ended PCR testing by the Clinical Laboratory to detect mutant strains and we started the detection of mutant strains *via* Sanger sequencing by the Center for Clinical Sciences. In December, we started analyzing the entire genome with whole-genome sequencing.

As Figure 1 shows, the number of tests increased significantly compared to the early days, and we are able to effectively control infection and manage beds.

Changes in the PCR testing methods used in the Clinical Laboratory

From March to May 2020, we conducted PCR testing using primers and probes provided by the National Institute of Infectious Diseases in Japan (NIID-J) (*1*). Making all of the reagent adjustments from scratch took a lot of time and great effort. Therefore, we had a very hard time using that approach as a routine testing method. To prevent contamination and human error, we spent a lot of time managing the environment and training the staff for testing.

In June, we adopted a new PCR testing method using LightMix® Modular SARS and Wuhan CoV N-gene and E-gene (LightMix, Roche). The testing

Table 1. Main events related to the PCR testing system for SARS-CoV-2 over the past two years

February, 2020	Start to consider an in-hospital PCR testing at this facility's Clinical Laboratory
March, 2020	Start to assist with specimen management at this facility's fever clinic Start of in-hospital PCR testing by the Clinical Laboratory (about 5 specimens per day only on weekdays) Expansion to in-hospital PCR testing on weekends and holidays
April, 2020	Expansion to two assays on weekdays and 40 specimens per day
May, 2020	Start of preoperative PCR testing and prepartum PCR testing
August, 2020	Start of urgent PCR testing, 24 hours a day in cooperation with the clinical technologist on the night shift in the Emergency Department
September, 2020	End of outsourced PCR testing and start of PCR testing by the Clinical Laboratory
December, 2020	Start of PCR testing for all hospitalized patients
January, 2021	Start of PCR testing for patient visitors Start of PCR testing for recipients of full medical checkups
March, 2021	Start of PCR testing to detect N501Y and E484K mutations of the SARS-CoV-2 spike protein
June, 2021	Addition of PCR testing to detect the L452R mutation of the SARS-CoV-2 spike protein
July, 2021	End of PCR testing by the Clinical Laboratory to detect mutant strains and start of detection of mutant strains *via* Sanger sequencing by the Center for Clinical Sciences
December, 2021	Start of analysis of the entire genome *via* whole-genome sequencing by the Center for Clinical Sciences

Modified from Reference 2 (*2*).

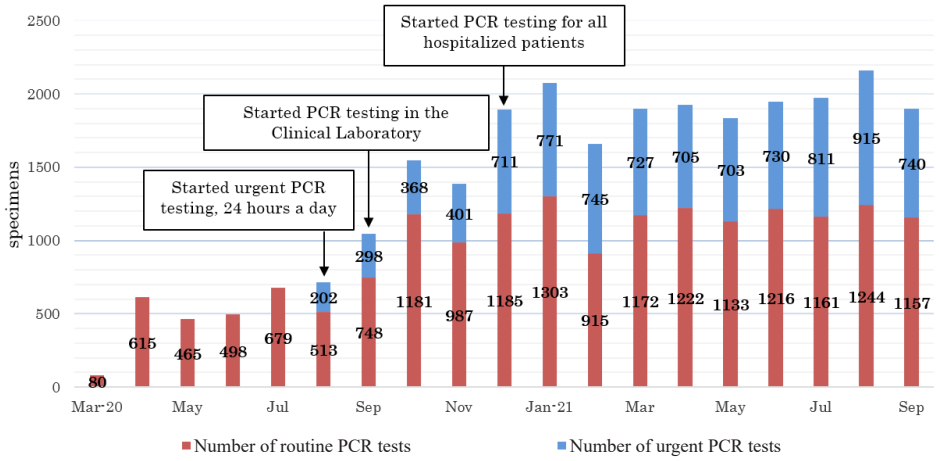

Figure 1. Number of tests conducted at this hospital. Modified from Reference 2 (*2*).

process was the same as before, but the PCR reaction time was much shorter (only one hour). The LightMix reagent adjustment was simpler than before. In addition, LightMix allowed us to measure the internal control and to prevent false negatives.

In July, we started using cobas SARS-CoV-2 (cobas, Roche), which can automatically conduct PCR testing on up to 94 specimens in one round. Therefore, this method greatly reduced the burden on the staff for testing.

In August, we adopted the Filmarray® Respiratory Panel 2.1 (Filmarray, BioMérieux), which takes only about an hour to complete. This allowed prompt reporting of each test result.

In December 2021, we introduced the Xpert Xpress SARS-CoV-2 'Cepheid' (Genexpert, Beckman Coulter), which we basically use for urgent PCR testing.

Currently, we have several other instruments and we are able to choose one based on the number of specimens and urgency.

Results of those changes

PCR testing consists of three major steps (1) extraction, (2) reagent preparation, and (3) amplification and detection. Before we started SARS-CoV-2 PCR testing, we used reagent kits for all PCR testing. Since the three processes were mostly automated before the start of SARS-CoV-2 PCR testing, we conducted the tests without highly specialized knowledge or skills. However, when the decision was made to conduct SARS-CoV-2 PCR testing in-house, we had to perform

(1) extraction and (2) reagent adjustment manually because no SARS-CoV-2 detection reagent kits were available for automated instruments. We did not have enough experience to conduct PCR testing manually. Therefore, we struggled with manual work, which required intense concentration, and we felt pressured to avoid contamination and mistakes. In April and May 2020 in particular, COVID-19 was spreading throughout Tokyo, and there was always a possibility that the staff for testing might be infected. Moreover, there was also a concern that we might face shortages of reagents and consumables for testing while the number of tests increased. However, we have gained valuable experience overcoming those difficulties.

As Figure 1 shows, we are able to test more than 2,000 specimens per month, using automated instruments to test large numbers of specimens. Moreover, we are able to conduct urgent PCR testing 24 hours a day in cooperation with the clinical technologist on the night shift in the Emergency Department.

We will continue to meet new needs for COVID-19 treatment with the cooperation of other departments.

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References

1. National Institute of Infectious Diseases. Manual for Pathogen Detection: 2019-nCoV Ver.2.9.1. *https://www.niid.go.jp/niid/images/lab-manual/2019-nCoV20200319.pdf* (accessed July 31, 2022). (in Japanese)
2. Motohashi A. The development of SARS-CoV-2 PCR testing methods in NCGM. In: The experiences and evidences of NCGM staff: New coronavirus infections COVID-19: 2020-2021 (National Center for Global Health and Medicine, eds). Public Relations and Planning Office, Department of Planning and Strategy, National Center for Global Health and Medicine, Tokyo, 2021; pp.109-113.

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LETTER
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Responding to COVID-19: Establishing a nursing system that is appropriate for the new post-epidemic era

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Abstract: Hospitals that admit patients with COVID-19 face the challenge of not only dealing with these patients but also balancing normal medical care and hospital management to cope with the challenges posed by the new post-epidemic era. Over the past two years of responding to COVID-19 as a front-line clinical nurse, my colleagues and I have fully appreciated the need to establish a nursing system that is appropriate for the new post-epidemic era. The following four aspects should be emphasized: *i*) the continuation of thorough infection control measures; *ii*) exploring new approaches to training for new recruits; *iii*) ensuring nursing workforce and improving the nursing capacity to cope with patients critically ill with COVID-19; and *iv*) teamwork and team care to provide nurses with timely psychological assistance.

***Keywords*:** COVID-19, nursing system, post-epidemic era, Japan

More than two years have passed since this Hospital – the Center Hospital of the National Center for Global Health and Medicine - began admitting patients with COVID-19 in January 2020. As a nurse manager, my colleagues and I have dealt with many things during this period that we experienced for the first time, including caring for patients in moderate to severe condition, setting up PCR testing sites, PCR testing for returnees on charter flights to Japan from Hubei, China (*1*), and dispatching medical personnel to the cruise ship Diamond Princess docked in Yokohama, Japan (Figure 1). Moreover, hospitals that admit patients with COVID-19 face the challenge of not only dealing with these patients but also balancing normal medical care and hospital management to cope with the challenges posed by the new post-epidemic era.

In terms of clinical practice, nursing system that is appropriate for the new post-epidemic era needs to be established. The following four aspects should be emphasized in that system.

First, given that the Nursing department is the department with the largest number of employees in a hospital, the continuation of thorough infection control measures is a key factor in preventing infection clusters among hospital employees (*2*). Infection control for nursing staff including the wear of protective clothing in the correct manner, hand washing and hand disinfection, and avoiding contact during breaks to maintain social distancing should be thoroughly implemented.

Second, the impact of the epidemic has reduced the number of patients admitted for other diseases and reduced opportunities for new nurses to receive clinical practice, so devising new approaches to training for new recruits will have a significant impact on the continuity of the nursing system. Training needs to include subjects such as infection prevention, nursing practice, and providing daily living and mental health support for new employees who feel burdened with work and life during the current COVID-19 epidemic.

Third, because of the high need for medical and nursing care in wards admitting patients with COVID-19, there is a need to ensure the nursing workforce on these wards and to improve the nursing capacity to cope with patients critically ill with COVID-19 (*3*). The coordinated management of caregivers is essential as the number of infected patients increases and decreases.

Forth, timely psychological assistance for nurses should be promoted. Due to the many unknowns regarding the virus, nurses are learning how to care for critically ill patients while developing anxiety and various difficulties that they have never experienced before (*4-7*), including increased fatigue from the increasing number of critically ill patients, challenges in handling critically ill patients, and coping with the anger and grief of patients and their families. In these situations, teamwork and team care are especially important.

In conclusion, over the past two years of responding to COVID-19 as a front-line clinical nurse, my colleagues and I have witnessed the considerably ability of nursing

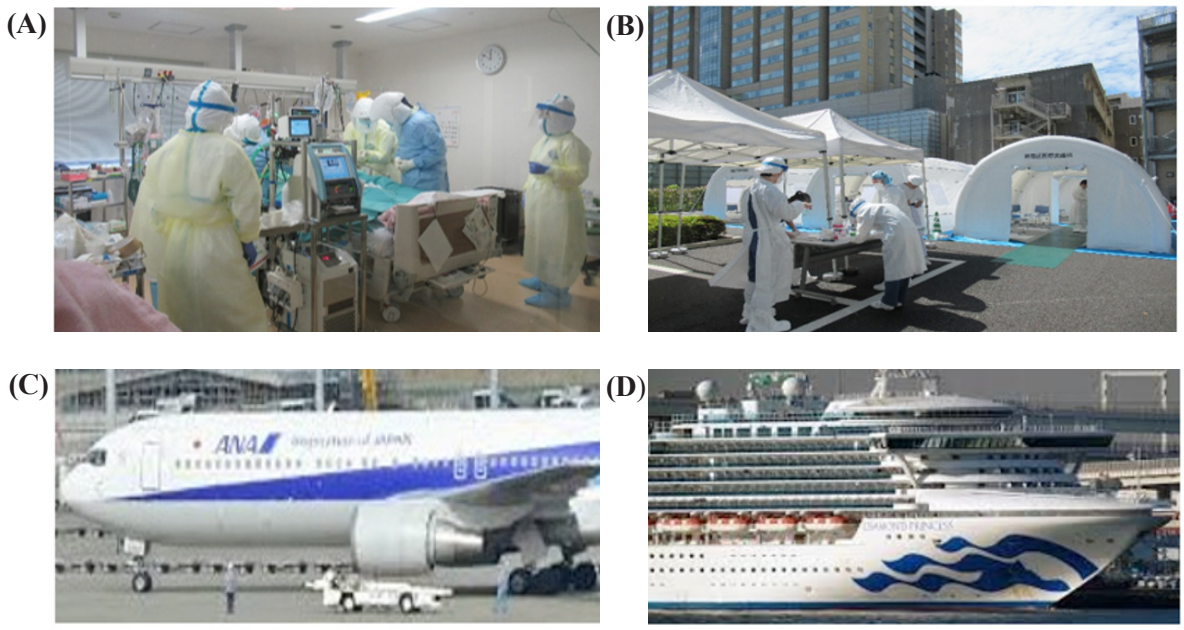

Figure 1. Challenges with nursing at our hospital since admitting COVID-19 patients. (A) caring for patients in moderate to severe condition; **(B)** setting up PCR testing sites; **(C)** a charter flight to Japan from Hubei, China; **(D)** the cruise ship Diamond Princess docked in Yokohama, Japan.

staff to cope with the situation, but nurses have also been placed under enormous stress that they would not be subjected to under normal circumstances. We are proud to play our part in the fight against the COVID-19 epidemic, and we call for the establishment of a nursing system that is appropriate for the new post-epidemic era to better respond to COVID-19 and unknown emerging infectious diseases in the future.

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Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. Hayakawa K, Kutsuna S, Kawamata T, *et al*. SARS-CoV-2 infection among returnees on charter flights to Japan from Hubei, China: a report from National Center for Global Health and Medicine. Glob Health Med. 2020; 2:107-111.
2. Umeda A, Sugiki Y. Nursing care for patients with COVID-19 on extracorporeal membrane oxygenation (ECMO) support. Glob Health Med. 2020; 2:127-130.
3. Lake ET. How effective response to COVID-19 relies on nursing research. Res Nurs Health. 2020; 43:213-214.
4. Mattila E, Peltokoski J, Neva MH, Kaunonen M, Helminen M, Parkkila AK. COVID-19: anxiety among hospital staff and associated factors. Ann Med. 2021; 53:237-246.
5. Lai J, Ma S, Wang Y, *et al*. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open. 2020; 3:e203976.
6. Nie A, Su X, Zhang S, Guan W, Li J. Psychological impact of COVID-19 outbreak on frontline nurses: A cross-sectional survey study. J Clin Nurs. 2020; 29:4217-4226.
7. Kang L, Ma S, Chen M, Yang J, Wang Y, Li R, Yao L, Bai H, Cai Z, Xiang Yang B, Hu S, Zhang K, Wang G, Ma C, Liu Z. Impact on mental health and perceptions of psychological care among medical and nursing staff in Wuhan during the 2019 novel coronavirus disease outbreak: A cross-sectional study. Brain Behav Immun. 2020; 87:11-17.

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LETTER

The role of clinical engineers in the coronavirus disease 2019 pandemic

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Abstract: The duties of a clinical engineer (CE) during the coronavirus infection 2019 (COVID-19) pandemic were diverse. The original duties of a CE included operation and maintenance of life support equipment used for respiratory therapy, hemodialysis, and extracorporeal membrane oxygenation. The management of life support equipment is critical. The PB-840 ventilator is equipped with a heat sink system that dissipates internal heat through thermal conduction. Therefore, internal contamination is less likely to occur. The exhalation filter used in the PB-840 can be used for up to 15 days. It can be used for long periods of time without maintenance, reducing the risk of infection. The PB-840 is a suitable device for patients with COVID-19. Its use in critically ill patients was determined to be a priority. Thus, use of an appropriate device for infection control requires a proper understanding of and familiarity with the device in question.

***Keywords*:** invasive ventilators, non-invasive ventilators (NIV), high-flow nasal cannulas (HFNC)

The work of clinical engineers (CE) during the COVID-19 pandemic includes operation and maintenance of life support equipment used for respiratory therapy, blood purification therapy, and extracorporeal membrane oxygenation. Plasma from patients recovering from COVID-19 (*1*) is also collected by CEs.

Internal contamination of the equipment after use is an issue faced by CEs. Most medical devices are equipped with cooling fans to cool the central processing unit (CPU) inside the device. If the cooling fan fails to function, the CPU is heated, and the device stops working. Though the cooling fan is equipped with a dust filter that filters room air, it is not equipped with filters against viruses. This may cause viral contamination inside the device. The survival period of the COVID-19 virus depends on the surface material it is attached to (*2*). Currently, the survival period of the virus inside medical devices remains unknown. The survival period of the virus appears to vary depending on the type of surface, temperature, humidity, and even sunlight (*3*). Contaminated equipment may cause a secondary infection upon cleaning and inspection or when it is used on another patient. We attached high-efficiency particulate air filters to cooling fans to prevent internal contamination. After use, the system was operated in a well-ventilated area to eliminate internal contamination. Regular equipment maintenance was also done.

The PB-840 ventilator (Medtronic, USA), an invasive ventilator used during the COVID-19 pandemic, contains a heat sink system that dissipates internal heat via thermal conduction rather than by a cooling fan. This reduces the chances of internal contamination. The exhalation filter used in the PB-840 can be used for a maximum of 15 days without maintenance, thereby, reducing the risk of infection. The PB-840 was deemed to be a suitable device for patients with COVID-19 and it was prioritized for use in critically ill patients.

The trends in use of invasive and non-invasive ventilators (NIV), and high-flow nasal cannulas (HFNC) in patients with COVID-19 are shown in Figure 1. At the beginning of the pandemic, use of NIVs and HFNCs decreased because they were thought to increase the risk of infection among medical personnel due to the dispersal of air exhaled by patients. However, a study conducted in December 2020 revealed that virus dispersal by this equipment was limited (*4*). Thereafter, the use of NIVs and HFNCs increased. Usage peaked during the fifth wave of the pandemic, and in August 2021, 10 patients were using the PB-840, 61 were using an NIV, and 51 patients were using an HFNC. Something that must be noted is that using NIVs and HFNCs poses a higher risk of environmental contamination than invasive ventilation using a closed suction system (*5*). Therefore, adequate care must be taken to prevent infection. Following the Centers for Disease Control and Prevention (CDC) guidelines (*6*), we ensured that personal protective equipment (PPE) was properly donned and removed by all COVID-19-positive patients under the guidance of

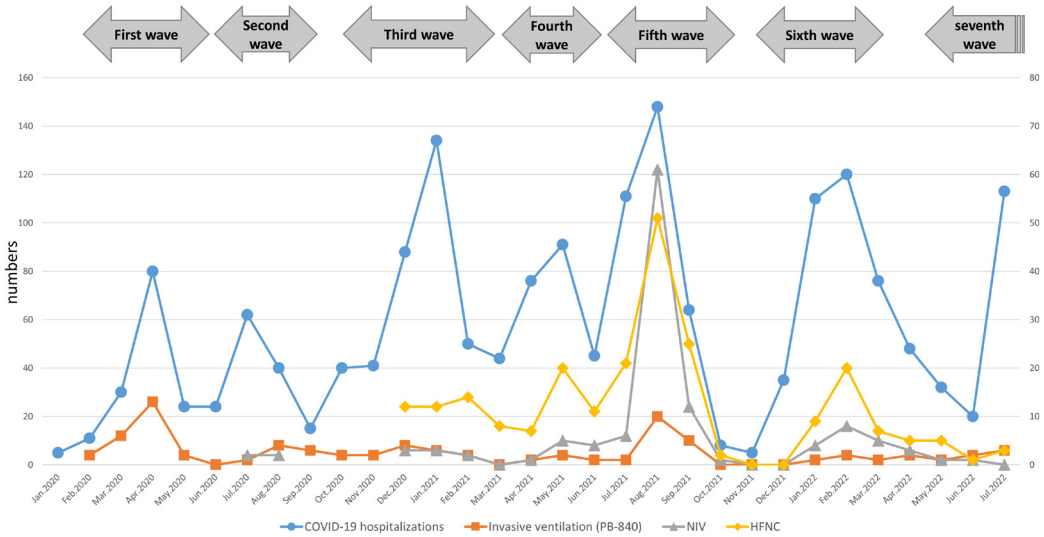

Figure 1. Trends in COVID-19 hospitalizations and artificial respiration therapy. August 2021 was the month with the highest number of patients receiving respiratory therapy; a total of 10 patients used the PB-840, 61 used an NIV, and 51 used an HFNC. Data are from the NCGM Center Hospital.

our infection control team (ICT).

In conclusion, CEs have a wide range of duties during the COVID-19 pandemic. They need to be well-versed in the use of required equipment in order to ensure that appropriate machines are used to treat a specific infection. Moreover, they need to maintain the equipment after each use to ensure the safety of its users and operators.

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

References

1. Terada M, Kutsuna S, Togano T, *et al*. How we secured a COVID-19 convalescent plasma procurement scheme in Japan. Transfusion. 2021; 61:1998-2007.
2. van Doremalen N, Bushmaker T, Morris DH, *et al*. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382:1564-1567.
3. Marzoli F, Bortolami A, Pezzuto A, Mazzetto E, Piro R, Terregino C, Bonfante F, Belluco S. A systematic review of human coronaviruses survival on environmental surfaces. Sci Total Environ. 2021; 778:146191.
4. Takazono T, Yamamoto K, Okamoto R, Morimoto S, Izumikawa K, Mukae H. Effects of surgical masks on droplet dispersion under various oxygen delivery modalities. Crit Care. 2021; 25:89.
5. Ahn JY, An S, Sohn Y, *et al*. Environmental contamination in the isolation rooms of COVID-19 patients with severe pneumonia requiring mechanical ventilation or high-flow oxygen therapy. J Hosp Infect. 2020; 106:570-576.
6. CDC. Sequence for putting on personal protective equipment (PPE). *https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf* (accessed February 28, 2022).

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