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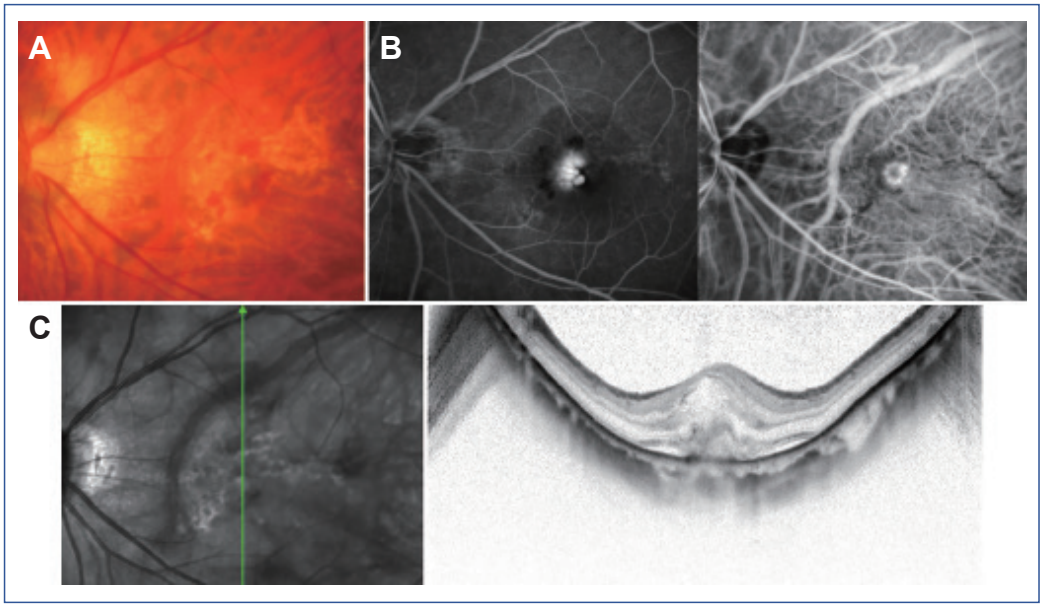

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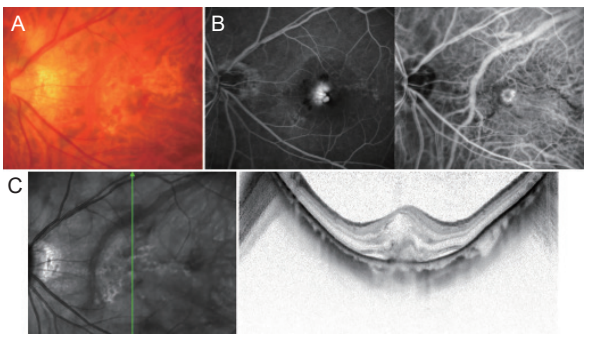

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Pathologic myopia: an overview of the current understanding and interventions

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Abstract: Pathologic myopia is a major cause of low vision and blindness worldwide. Its social and economic burden has been demonstrated by epidemiological studies. There have been recent advances in the classification system for myopic maculopathy that enables clinicians to describe different types of lesions, including tessellated fundus, diffuse/patchy chorioretinal atrophy, macular atrophy, lacquer cracks, choroidal neovascularization (CNV), and Fuchs' spot, in a standardized format. From a therapeutic point of view, anti-vascular endothelial growth factor therapy has been established as first-line choice for myopic CNV. For myopic retinoschisis and macular holes with/without retinal detachment, pars plana vitrectomy has been generally accepted as an efficient strategy. Studies are being conducted to determine how to avoid the development of a postoperative macular hole and to improve the quality of vision after surgery. In recent years, studies have revealed preventive measures that can be taken against myopia progression, including low-dose atropine eyedrops and contact lens wearing with peripheral myopic defocusing.

***Keywords*:** pathologic myopia, myopic maculopathy, myopic choroidal neovascularization, myopic retinoschisis

Introduction

Myopia has been a globally prevalent health issue and the incidence of myopia is expected to increase in the next few decades. Myopia is defined as refractive error by which the image coming into the eye is focused in front of, but not on, the retina. Both genetic and environmental factors are considered to play important roles in its development. In high myopic eyes, pathologic myopia, also known as "myopic macular degeneration", "myopic maculopathy", or "degenerative myopia" can occur, which can lead to visual acuity (VA) decline. Pathologic myopia affects 1-3% of the general population (*1*) and has been one of the major causes of low vision and blindness worldwide. In addition, because pathologic myopia often affects the productive age population, it is considered to be a social and economic burden.

In this review, current knowledge is summarized on the epidemiology of myopia, classification of myopic maculopathy, myopic choroidal neovascularization, myopic retinoschisis, and macular holes as well as interventions to suppress myopia progression.

Epidemiology of myopia

Epidemiology studies on myopia have been conducted in multiple locations around the world, and the reported prevalence and its impact on low vision and blindness have varied among the studies. Here are some examples.

A report from the Blue Mountains Eye Study that was conducted in Australia and published in 2002 investigated the prevalence of myopia and myopic retinopathy (*2*). In this urban population, aged 49 years or older, myopia was defined as < −1.0 D and was observed in 17% of the total participants. High myopia was defined as < −5.0 D and was observed in 2.7%. In this study, myopic retinopathy was defined as a staphyloma, lacquer cracks, Fuchs' spot and myopic chorioretinal atrophy (CRA). Myopic retinopathy was observed in 1.2% of the population. The cases with myopic retinopathy were followed and significant progression was detected at re-examination after 5 years in 17% with an average deteriorated VA of nearly 2 logMAR lines (*2*).

In a report from the Rotterdam Study published in 1998, pathologic myopia was the third leading (6%) cause of blindness and also the third leading (6%) cause of low vision in subjects aged 55 years or older (*3*).

In a report from the Tajimi Study published in 2006, subjects aged 40 years or older were enrolled and high myopia of < −5.0 D was found in 8% of the participants, myopic macular degeneration was the third leading (9.2%) cause of bilateral or monocular low vision and the first leading (22.4%) cause of bilateral or monocular blindness (*4*).

In a report from the Beijing Eye Study published in 2006, degenerative myopia was responsible for the second leading (32.7%) cause of low vision and also the second leading (7.7%) cause of blindness. Cataract was

the most frequent cause of both low vision and blindness. Myopia was the most frequent cause of both low vision and blindness in a population aged 40-49 years (*5*).

In the United States, the prevalence of myopia was 24% in the population aged 40 years and older (*i.e.*, 34 million people), but it varied depending on ethnicity. The highest prevalence was for Caucasians (26%), and lower for Hispanics (18%), and African-Americans (15%). Moreover, myopia prevalence is predicted to increase by 2050 such that there will likely be 45 million people aged 40 years and older affected (*6*).

In 2015, Rudnicka *et al.* reported results from a meta-analysis study that used quantitative Bayesian meta-regression on data from previous studies. The statistical model analyzed the prevalence of myopia (defined as < −0.5 D) for different ages and ethnicities around the world, which constantly changes over time (*7*). The meta-analysis comprised 143 articles including over 350,000 subjects with more than 74,000 myopic cases. It disclosed the differences in myopia prevalence depending on ethnicity, age, environment, and gender. For example, myopia is most prevalent in East Asians, and at the age of 10 years old, the prevalence was already 35%. At the age of 18 years old, the prevalence was as high as 80% in East Asians, while it was less prevalent in Caucasians (23%) and black Africans (6%). Children in an urban environment have 2.6-fold higher risk for developing myopia compared to those in a rural environment, and girls seem to have a 2-fold higher risk for developing myopia than boys, at least in Caucasians and East Asians (*7*).

While myopia itself is a major cause of vision loss, as described in these epidemiological studies, myopia also contributes to another vision-threatening disease; that is, glaucoma. Myopia is a risk factor for the development of glaucoma, and a previous meta-analysis has estimated that pooled odds for developing glaucoma is 1.65 and 2.46 for low and high myopic eyes, respectively (*8*). Therefore, detecting glaucoma in myopic eyes is important. This is often a diagnostic challenge for clinicians, however, due to myopic distortion and deformation in the optic nerve head and peri-papillary tissues (*9*). To diagnose myopic glaucoma, multimodal examinations through structural imaging and functional visual field tests are useful, however, care needs to be taken because they may increase the number of false diagnoses with glaucoma (*9*).

Classification of myopic maculopathy

High myopia is commonly defined as refractive error of −5.0 D or −6.0 D and/or axial length longer than 26.0 mm or 26.5 mm. Pathologic myopia is highly myopic eyes with degenerative macular changes that present with different patterns and degrees of chorioretinal atrophy and specific findings including lacquer cracks, myopic CNV, and Fuchs' spot. Curtin *et al.* first reported the classification of myopic maculopathy in 1970 (*10*), and classifications have also been proposed by Avila *et al.* (*11*) and Hayashi *et al.* (*12*). However, international consensus on the classification of myopic maculopathy did not exist until a report published in 2015 described the classifications at an international consensus meeting (*13*). In this study, Ohno-Matsui *et al.* conducted a meta-analysis for pathologic myopia (META-PM) and proposed a new grading system for myopic maculopathy (Table 1, Figure 1) that was based on the long-term risk to develop myopic CNV and macular atrophy (*14*). Lacquer cracks, myopic CNV, and Fuchs' spot were defined as "plus" signs that are features that can lead to central vision loss.

Myopic choroidal neovascularization (CNV)

Myopic CNV is a serious complication in pathologic myopia that affects central vision (Figure 2). It recurs frequently and is usually bilateral. The long-term prognosis is poor, even if treated (*15*). The prevalence of myopic CNV is largely unknown, but a recent study based on the National Health and Nutrition Examination Survey and the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS®) Registry has estimated the prevalence among people aged 18 years and older in the United States as 0.017% (95% CI, 0.010-0.030) (*16*). The pathogenesis of myopic CNV is still largely unknown, but vascular endothelial growth factor (VEGF) levels in the aqueous humor are known to be elevated (*15*).

The funduscopic findings in myopic CNV can be staged as active, scarring, and atrophic, as classified by Tokoro in 1998 (*17*). Active myopic CNV is active neovessel formation that often occurs with a subretinal hemorrhage. For monitoring disease activity and decisions on re-treatment, VA, fluorescein angiography, and optical coherence tomography (OCT) are the vital examinations. Myopic CNV can lead to a scar formation with a hyperpigmented Fuchs' spot. In the long run, the macula becomes atrophic, forming CRA. Due to degenerative CRA progression in the atrophic stage, the eyes with myopic CNV undergo gradual VA decline over time even if the neovascular activity is successfully suppressed by treatment (*15*).

Regarding treatment for myopic CNV, intravitreal injections of anti-VEGF agents, including ranibizumab, aflibercept, or bevacizumab, have been the gold standard, which has been established through randomized controlled trials (*18-20*). The established regimen of anti-VEGF therapy is an initial injection followed by an additional injection when necessary, which is called the 1+ pro re nata regimen (*15*). However, of note, the advantage gained through anti-VEGF therapy is sustained for the initial several years, but it can gradually decline, and after 5-6 years, most of the VA gain might be lost (*21*). In the case that

Table 1. Classification of myopic maculopathy based on international consensus meeting (*13*).

Category	Description
1: Tessellated fundus	Well-defined choroidal vessels around the fovea and the arcade vessels.
2: Diffuse CRA	Yellowish white appearance of posterior pole.
3: Patchy CRA	Well-defined, grayish white lesions in the macular area or around the optic disc.
4: Macular atrophy	Well-defined, grayish white or whitish, round chorioretinal atrophic lesion in the foveal region.
"Plus" lesions	
Lacquer cracks	Breaks of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris complex.
CNV	Exudation, hemorrhage, or serous retinal detachment at the posterior pole.
Fuchs' spot	Pigmented grayish white scar of myopic CNV without associated exudation.

The categories are in the order for long-term risk to develop myopic CNV and macular atrophy. "Plus" lesions are the additional features of myopic maculopathy that leads to visual loss regardless of the categorical stages.

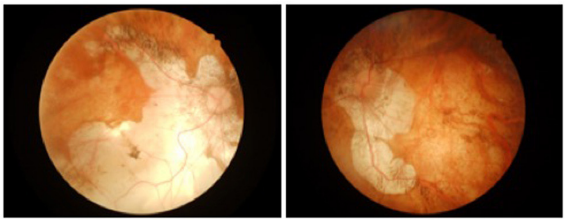

Figure 1. Fundus photographs of a patient with pathologic myopia. Both eyes are at the stage of macular atrophy (Category 4) associated with tessellated fundus, diffuse and patchy CRAs.

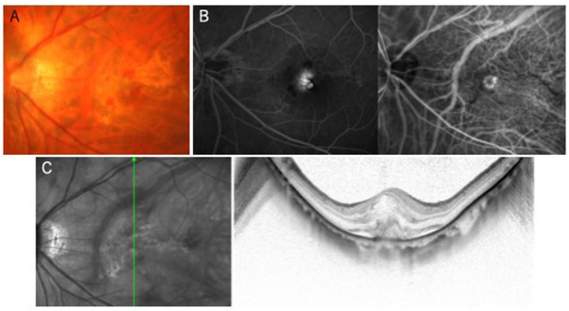

Figure 2. myopic CNV. (A) Color fundus photograph; (B) fluorescein (left) and indocyanine green (right) angiography; and (C) optical coherence tomography.

anti-VEGF therapy cannot be performed, verteporfin photodynamic therapy is an alternative choice of treatment, although the therapeutic effect is inferior.

Myopic retinoschisis (MRS) and macular hole (MH)

In high myopic eyes, typically with a posterior staphyloma, MRS can develop and lead to severe loss of VA. Retinoschisis is easily visualized on OCT, and MRS is observed in the outer retina, but it sometimes occurs both in the inner and outer retina. Regarding the pathogenesis of MRS, in addition to the posterior traction by a staphyloma, anterior traction by the epiretinal membrane (ERM) or adhesive vitreous cortex is considered to play an important role in the development of MRS (*22*). MRS is further associated with the development of a full-thickness MH with/without macular retinal detachment. These pathologies need to be treated surgically, and should not be performed late since long-standing MRS, even if successfully treated, does not result in sufficient postoperative visual recovery.

Standard surgical procedures used to treat MRS are pars plana vitrectomy with ERM removal plus inner limiting membrane (ILM) peeling. However, the postoperative course could be complicated by the development of a full-thickness MH, for which several reports have recently suggested modifications of the surgical procedures. Described below is fovea-sparing ILM peeling and scleral imbrication.

The main purpose of fovea-sparing ILM peeling is to prevent the development of a postoperative full-thickness MH with or without retinal detachment, this surgical technique was first reported by Shimada *et al.* in 2012 (*23*). In this study, a full-thickness MH developed in 5 of 30 eyes (16.7%) in which total ILM peeling was performed for MRS, whereas it developed in 0 of 15 eyes in which fovea-sparing ILM peeling was performed. In addition, postoperative VA was superior in eyes with fovea-sparing ILM peeling. Similar results have been reported in two other studies (*24,25*), however, a recent study has argued that there was no difference in the postoperative VA between fovea-sparing and complete ILM peeling groups and that the rate of postoperative MH development was not significant (2/20 *vs.* 0/13; $p = 0.508$) (*26*). The potential benefit of fovea-sparing ILM peeling compared to complete ILM peeling has not been established yet and this needs to be addressed in the future.

The other modification in the surgical treatment for MRS is the use of scleral imbrication. Swan first reported this surgical technique for retinal detachment in 1959, and it has been applied to MH retinal detachment (*27*) and MRS (*28*). Baba *et al.* reported the application of scleral imbrication to MRS with PPV but without ILM peeling. They suggested that since postoperative full-thickness MH development is attributed to ILM peeling, scleral imbrication without ILM peeling can be an option other than fovea-sparing ILM peeling. The axial length reduction that scleral imbrication confers is not large (less than 1 mm after a year postoperatively), but the procedure could change the shape of the posterior globe and flatten the steep curvature of a staphyloma (*28*), which might help resolve MRS and prevent the development of a full-

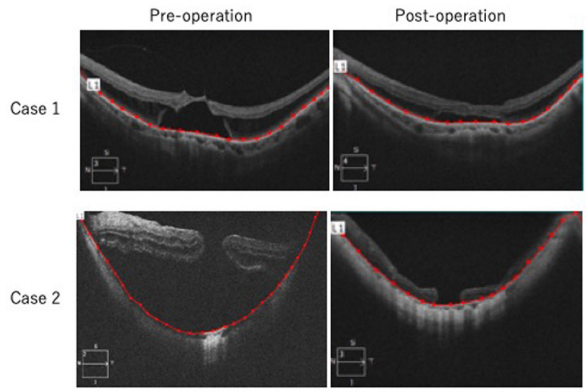

Figure 3. Flattened curvature of posterior fundus after lamellar scleral resection and infolding of the remaining sclera in patients with myopic retinoschisis and macular hole retinal detachment. Pre- and post-operative OCT in case 1 and 2 are shown. Posterior segment distance defined as the distance of retinal pigment epithelial line (red) using photo analyzer (AreaQ, Japan). Shorter posterior segment distance suggests flattened curvature of the posterior fundus after surgery.

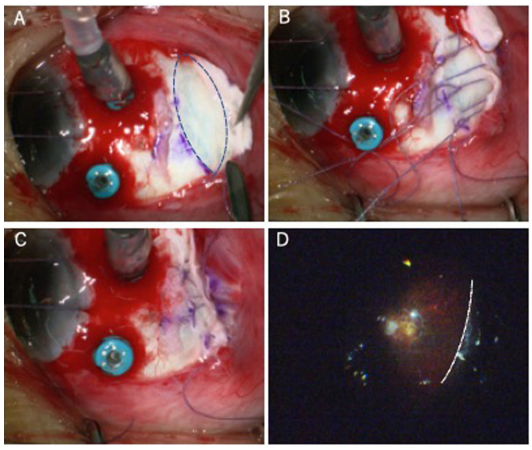

Figure 4. Intraoperative views of scleral shortening through scleral invagination with lamellar scleral resection to treat myopic retinoschisis. Dotted line in **(A)** indicates the area of lamellar scleral resection; **(B)** and **(C)** shows the infolding of the remaining sclera; dotted line in **(D)** indicates the infolded retina from inside of the eye under wide viewing system.

thickness MH (Figure 3).

A drawback of scleral imbrication is that a significant postoperative astigmatism (about 4.0 D worse at 1 month postoperatively and 2.0-3.0 D worse after 12 months compared to astigmatism before surgery) may develop (*27,28*). Instead of scleral imbrication, our team uses scleral shortening through scleral invagination with lamellar scleral resection (*29*) (Figure 4), which usually causes less postoperative astigmatism.

Suppression of myopia progression

While medical and surgical therapies for pathologic myopia are important, the ultimate goal is suppression of myopia progression, which could lead to a significant reduction of eyes with pathologic myopia. Studies have revealed modifiable factors for the progression of myopia (*30*). For example, time spent outdoors, which is related to less dopamine release, is considered to suppress myopia progression. Indeed, low-dose anti-muscarinic atropine eyedrops have been shown effective to suppress myopia (*31*). The other factor for myopia progression is peripheral hyperopic defocus. Not only recent studies have shown that orthokeratology (*32*) can reduce peripheral hyperopic defocusing and suppress myopia progression, but also a special contact lens that confers peripheral myopic defocusing has just been approved by Food and Drug Administration to be used for the suppression of myopia progression in children (*33*). However, long-term effectiveness and safety issues still remain (*30*).

Conclusions

In recent decades, remarkable advances have been made in understanding both the pathological basis and therapeutic strategies for pathologic myopia. Not only are studies being performed to improve currently available therapies, but also novel therapies to suppress the progression of pathologic myopia are being considered for future studies.

Acknowledgements

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Present status and perspective of chemotherapy for patients with unresectable advanced or metastatic gastric cancer in Japan

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Abstract: Patients with unresectable advanced or recurrent gastric cancer have a poor prognosis with overall survival times increasing by only a few months after anti-cancer drug therapy in the last four decades. The survival times from previous clinical trials for untreated metastatic gastric cancer in Japan are generally better than those reported from trials in European and North or South American countries. Therefore, the proportion of Japanese patients enrolled in recent global trials of novel anti-cancer drugs should be increased in order to identify drugs that specifically prolong the survival of such patients. S-1 plus oxaliplatin (SOX) therapy is the most commonly used standard first-line treatment for advanced gastric cancer in Japan. SOX induces mild nausea and vomiting, even in elderly patients, that can be treated by maintaining oral intake with adequate anti-emetic treatment usually given in an outpatient clinic. Neutropenia, nausea, and vomiting in SOX therapy were more frequently observed in female patients compared with males. Intensive toxic chemotherapy such as triplet therapy never prolonged overall survival or maintained a favorable quality of life. The current strategies used against metastatic gastric cancer need to be modified in regard to innovative treatments with current drugs, keeping in mind each categorized treatment population. In a real world of a diverse society even if the same treatment is performed, the outcome of the individual patient is different. It is important for each society to implement established treatment, knowing that the evidence from global trials aimed at drug approval does not necessarily show external validity.

***Keywords*:** gastric cancer, capecitabine, S-1, oxaliplatin, sex difference, ERCC1

Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide. In 2018, one million new cases of gastric cancer were diagnosed and 0.8 million cancer-related deaths occurred worldwide; of these, three quarters occurred in Asia, especially in East Asia (*1*).

The prevalence and mortality rate for gastric cancer has previously been high in Japan, and the age-adjusted mortality rate has decreased significantly in the last four decades, similar to what has been observed in the United States and Western European countries since 1940 (*2,3*) (Figure 1 and Figure 2). The cause of this drop in incidence is thought to be an increase in fresh food intake, such as raw vegetables and fruits, due to the increased storage of food products because of refrigeration, a decrease in salty food intake, and a decrease in *Helicobacter pylori* infection (*4*).

Since gastric cancer, in its early stages, is often asymptomatic, it is frequently diagnosed at an advanced stage in the absence of mass screening or the active surveillance of a population. In 1995-2000, 53% of Japanese gastric cancers were localized when diagnosed, which is comparatively high against the 27% reported by the US Surveillance, Epidemiology, and End Results program (*4*).

The age-adjusted survival rates of gastric cancer between 2005 and 2009 were higher in Japan (54%) and South Korea (58%) than in Western countries (18-31%) (*5*). The survival rate for this disease has increased along with the number of trained doctors who can perform gastroscopies, allowing convenient access to clinics and hospitals for many people; however, an increase in the number of cases detected by mass screening has not occurred (*6*). The proportions of patients with pathological stage (Japanese Gastric Cancer Association) IA, IB, II, IIIA, IIIB, and IV disease between 2001 and 2007 in Japan were 44.0%, 14.7%, 11.7%, 9.5%, 5.0%, and 12.4% respectively. The 5-year overall survival rates of patients with pathological stage IA, IB, II, IIIA, IIIB, and IV disease were 91.5%, 83.6%, 70.6%, 53.6%, 34.8%, and 16.4%. The 5-year survival rate was 42% and the proportion of pT1 was 22% between 1963 and 1969.

The number of patients with early gastric cancer has increased, however, the total number of deaths due to gastric cancer in Japan has not decreased because of the increase of the elderly population (Figure 3) (*7,8*). It is also important for progress in quality of medicine

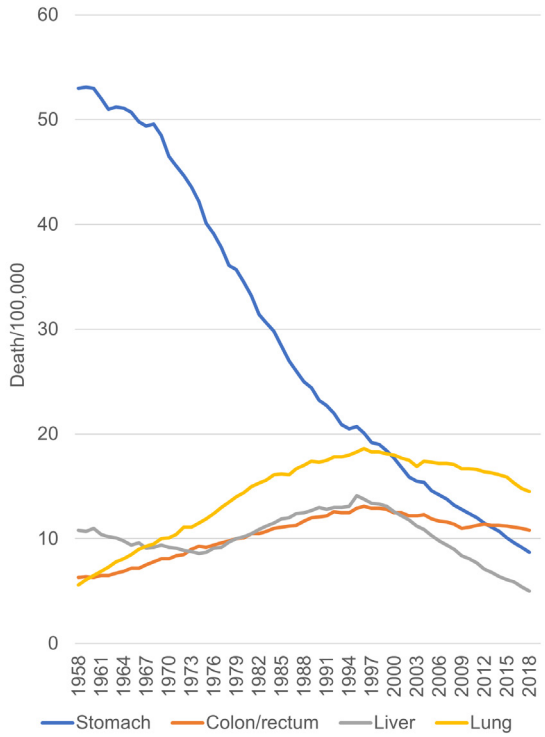

Figure 1. Trends in age-adjusted mortality rate of cancer of stomach, colorectum, liver, and lung in Japan, 1958-2018 (*3*). Gastric cancer showed a clear continuous decrease from 1960s.

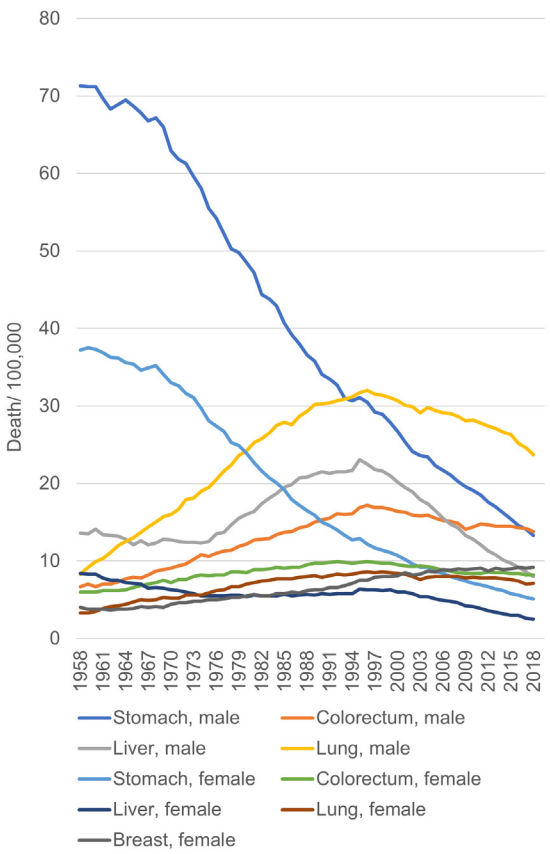

Figure 2. Trends in age-adjusted mortality rate of cancer of stomach, colorectum, liver, lung, and breast by sex in Japan, 1958-2018 (*3*). Gastric cancer showed a clear continuous decrease from 1960s in both male and female.

to improve both healthcare access and quality of health care across service areas and for all populations under universal health coverage by the public insurance system (*9*).

Despite a marked improvement in survival from gastric cancer in Japan through early detection, those who undergo surgical resection with systematic lymph node dissection and adjuvant chemotherapy, as well as patients with unresectable advanced or recurrent gastric cancer, have a poor prognosis. The development of more effective standard chemotherapies is therefore critical.

Prognosis in unresectable advanced or metastatic gastric cancer

The survival times from previous clinical trials for untreated advanced gastric cancer in Japan are generally better than those reported from trials in European and North or South American countries. The longer survival times of Japanese trials would be related to a higher proportion of patients having good prognostic factors such as a better performance status or prior gastrectomy (*10,11*) (Figure 4). Having a small tumor burden is also a good prognostic factor as well as subsequent chemotherapy after the failure of first-line treatment. A Korean phase III trial showed that the effect of second-line chemotherapy led to a slight improvement in post-progression survival and overall survival (OS) time (*12*). In particular, the survival times of East Asian patients with metastatic gastric cancer tended to be close to those of Japanese patients (*10,11,13*).

In AVAGST trial which was an international, randomized, placebo-controlled phase III study of chemotherapy with or without bevacizumab as first-line therapy for patients with advanced gastric cancer, the median duration of overall survival for patients treated with cisplatin 80 mg/m^2 plus capecitabine (1,000 mg/m^2 orally bid days 1-14) or 5-fluorouracil (5-FU) (800 mg/m^2/day continuous IV infusion days 1-5) every 3 weeks was 7.3 months (95% confidence interval (CI), 6.4-8.7) in Eastern Europe/South America, 9.1 months (95% CI, 6.9-14.4) in US/Western Europe, 11.6 months (95% CI, 9.1-15.6) in Korea and other Asian countries, and 14.1 months (95% CI, 10.9-17.6) in Japan. The hazard ratios (HR) for overall survival for each region when compared against US/Western Europe were 1.47 (95% CI, 1.09-1.99) for Eastern Europe/South America, 0.91 (95% CI, 0.67-1.25) for Korea and other Asian countries, and 0.87 (95% CI, 0.64-1.19) for Japan. Median progression-free survival by region was 4.4 months (95% CI, 4.0-5.4) in Eastern Europe/South America, 4.4 months (95% CI, 4.0-5.7) in US/Western Europe, 5.6 months (95% CI, 4.8-6.5) in Korea and other Asian countries, and 5.7

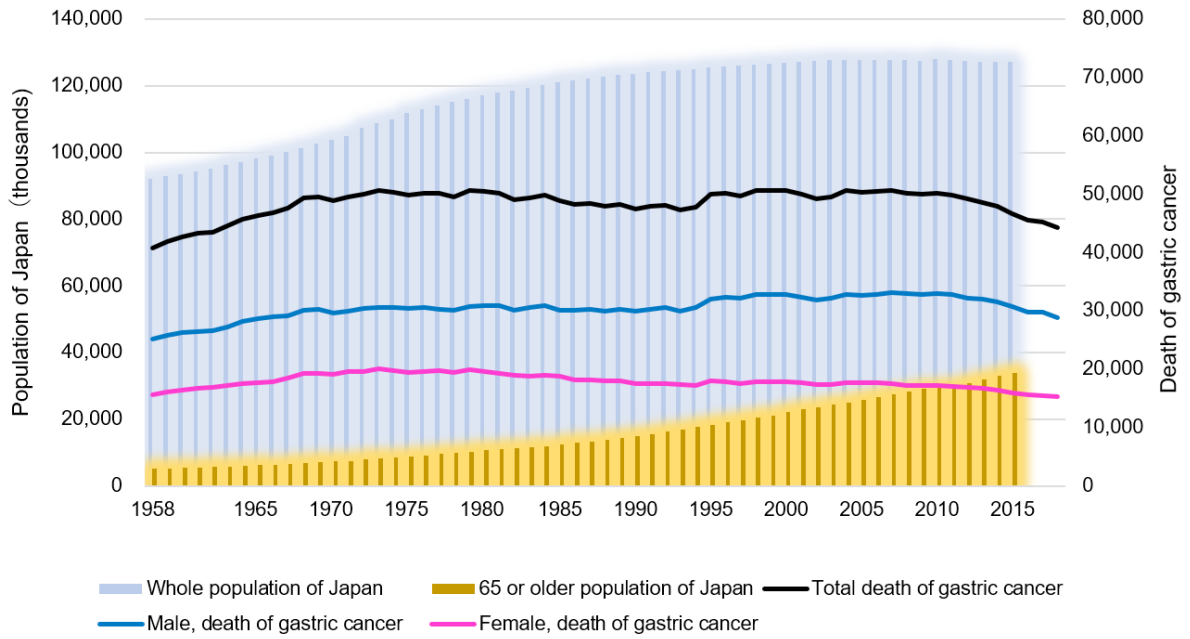

Figure 3. Trends in the number of death due to gastric cancer in Japan (*7,8*). The number of death due to gastric cancer has not decreased because of the increase of 65 or older population.

months (95% CI, 5.1-7.0) in Japan. Therefore, crucial trials of novel drugs should be undertaken mainly as East Asian trials rather than as global trials that include Central and Eastern European or South American countries (*10,11,13*). The final results for the latter would be expected to differ because the survival time of patients with gastric cancer in such countries were relatively shorter compared to those of patients in East Asian countries.

In recent global trials, the proportion of enrolled Japanese patients was capped at approximately 20% (*10,14,15*). However, this should be changed to decrease the ratio of patients entered into trials from European and American countries in order to identify drugs that specifically prolong the survival of Japanese and other East Asian patients. This is because of the difference in post-progression survival time after the failure of test treatments. The survival effect is also weakened in populations with longer survival times, resulting in different outcomes between East Asia and the rest of the world (*16*).

Standard first-line treatment in Japan

S-1 plus cisplatin (CS) is considered a standard first-line therapy based on the results of a randomized trial, Japan Clinical Oncology Group (JCOG) 9912, comparing oral S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine drug, with the continuous infusion of 5-FU and the SPIRITS trial, which highlighted the superiority of CS to S-1 in OS (*17,18*).

Globally, capecitabine plus cisplatin showed no inferiority to cisplatin plus 5-FU (*19*). Furthermore, oxaliplatin showed comparable activities to cisplatin in two phase III trials conducted in Europe (*20,21*). The Japanese G-SOX study also demonstrated comparable results in both progression-free survival (PFS) and OS between treatments with S-1 plus oxaliplatin (SOX) and CS (*22*). In the SOX regimen, S-1 was given orally for the first 2 weeks of a 3-week cycle, and oxaliplatin was infused at 100 mg/m^2 on day 1. In the CS regimen, S-1 was given for the first 3 weeks of a 5-week cycle, and cisplatin was administered at 60 mg/m^2 on day 8.

Thus, oral fluoropyrimidine plus platinum has been recognized worldwide as a standard chemotherapy for patients with human epidermal growth factor receptor 2 negative gastric cancer. Although significant differences in PFS and OS were not observed between elderly and non-elderly patients for SOX and CS, SOX showed better trends in PFS (HR, 0.805; 95% CI, 0.588-1.102) and OS (HR, 0.857; 95% CI, 0.629-1.167) compared with CS (*23*).

Management of chemotherapy in diverse patients

Regimens with cisplatin at more than 50 mg/m^2 have usually been administered as inpatient chemotherapy because these are highly emetic and require intensive hydration (*24*). However, cisplatin is known to be commonly administered as outpatient chemotherapy in other countries. This results in a decrease in the quality of life of patients and imposes a large financial burden due to the hospitalization cost.

The completion rate for two cycles of CS as an outpatient was found to be 78% (90% CI, 63-89), even in patients who were known to drink more than 1,500

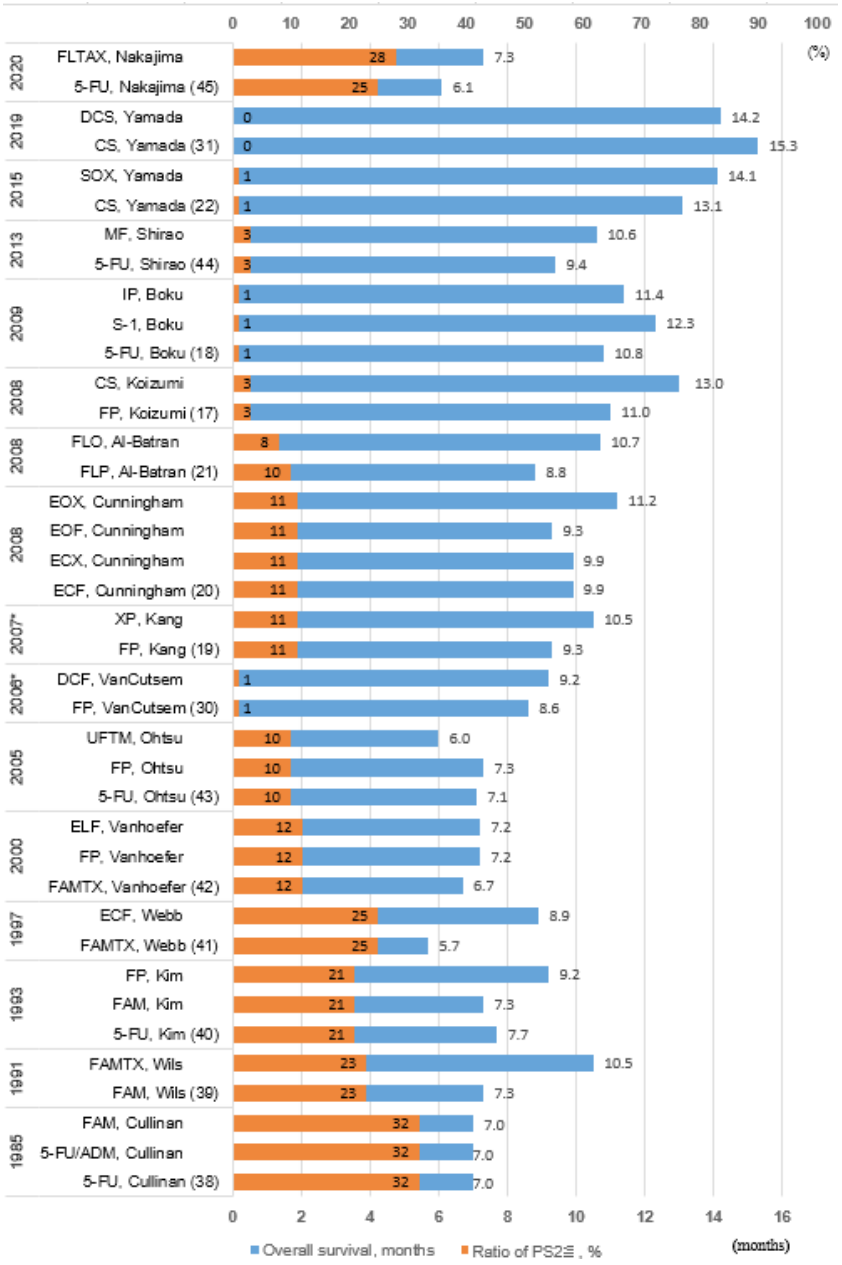

Figure 4. Overall survival of unresectable advanced/metastatic gastric cancer. The number of patients with poor performance 2 or more (*Karnofsky performance status < 80%) has decreased and the overall survival time has been over a year in recent trials. The target population was patients with peritoneal dissemination and/or ascites in articles doi: 10.1093/jjco/hyt114 and doi: 10.1007/s10120-020-01043-x. 5-FU, 5-fluorouracil; ADM, doxorubicin; CS, cisplatin/S-1; DCF, docetaxel/cisplatin/5-FU; DCS, docetaxel/cisplatin/S-1; ECF, epirubicin/cisplatin/5-FU; ECX; epirubicin/cisplatin/capecitabine; ELF, etoposide/leucovorin/5-FU; EOF, epirubcin/oxaliplatin/capecitabine; EOX, epirubicin/oxaliplatin/capecitabine; FAM, 5-FU/doxorubicin/mitomycin C; FAMTX, 5-FU/doxorubicin/methotrexate; FLO, 5-FU/leucovorin/oxaliplatin; FLP, 5-FU/leucovorin/cisplatin;FLTAX, 5-FU//-leucovorin/paclitaxel; FP, 5-FU/cisplatin; MF, methotrexate/5-FU; SOX, S-1/oxaliplatin; UFTM, tegafur/uracil/mitomycin C; XP, capecitabine/cisplatin.

mL per day before the start of CS therapy, in a feasibility study of relatively younger patients with advanced gastric cancer and a median age of 62 (range, 34 to 75). Of seven in 32 patients (22%) who did not complete the CS therapy, six continued CS as inpatient chemotherapy with intravenous hydration from the subsequent cycle. However, one was forced to switch to S-1 monotherapy due to grade 3 anorexia, nausea, and diarrhea. CS is not a feasible treatment for many elderly patients in an outpatient setting in clinical practice, while the number of patients who cannot tolerate CS in our rapidly aging society is increasing. Over time, the average age of death due to gastric cancer has increased from 61 years in 1950 to 73 in 2000 (*4*).

In addition, patients of working age require convenient therapy with mild toxicities that results in a short hospital stay, and at a lower cost. The Ministry of Labour, Health, and Welfare strongly supports the treatment of workers with cancer using anti-cancer agents by developing initiatives such as a "Plan to Accelerate Cancer Control Programs" in Dec. 2015 and subsequently a "Third Basic Plan to Promote Cancer

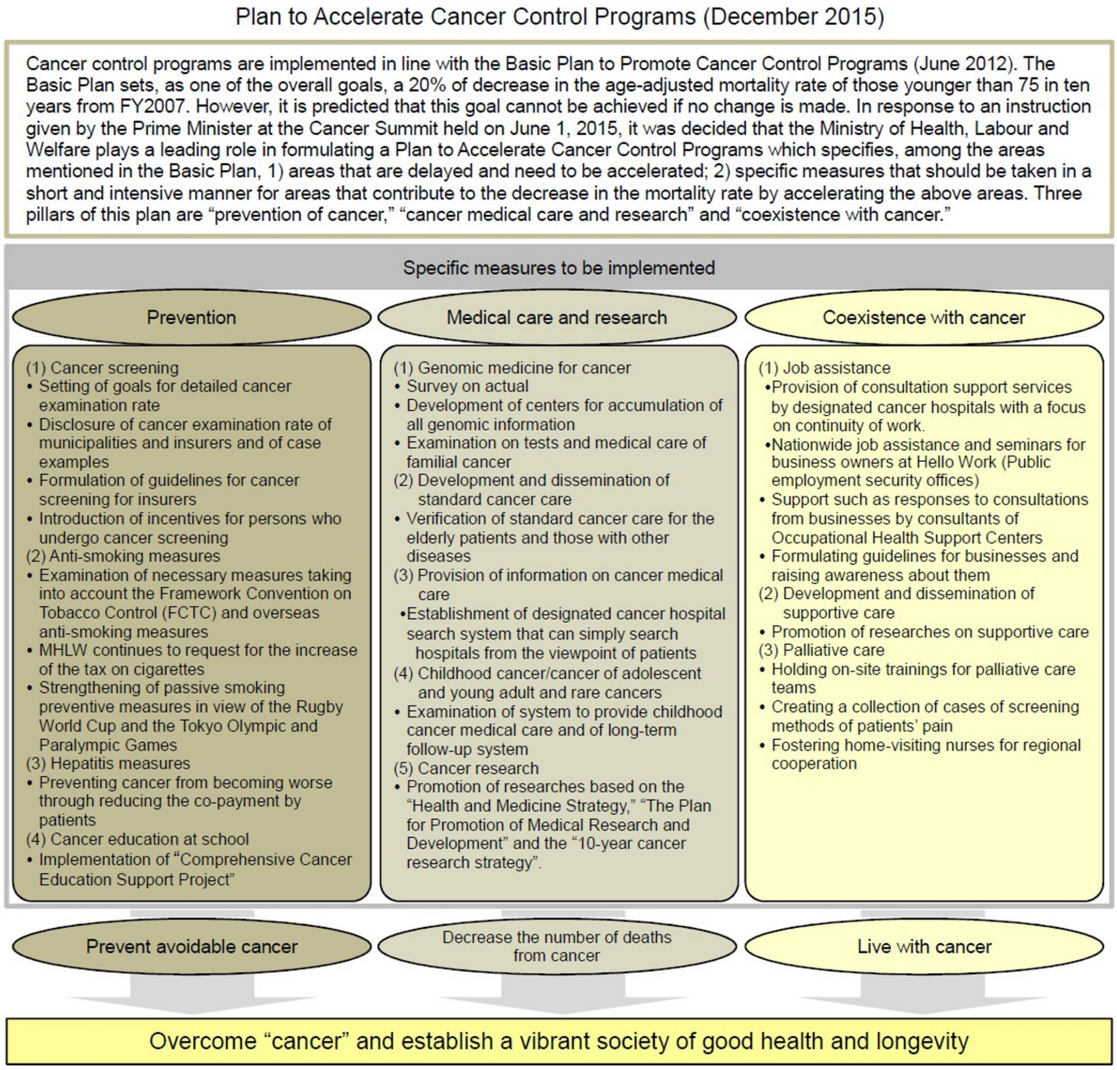

Figure 5. Plan to accelerate cancer control programs (*25,26*).

Control Programs", from Mar. 2018 (*25,26*) (Figure 5). The treatment of gastric cancer with SOX therapy, which does not require hydration, induces mild nausea and vomiting in patients that can be treated by maintaining their oral intake with adequate anti-emetic treatment usually given in our outpatient clinic.

Leukopenia, neutropenia, nausea, and vomiting during the first cycle of SOX treatment, then vomiting and stomatitis during the first cycle of CS were more frequently observed in female patients compared with males (*27*). On the other hand, a difference in drug efficacy was not observed between females and males undergoing either regimen. Therefore, intensive anti-emetic therapy with an aprepitant, consequent dexamethasone on day 2 to 3 and olanzapine should be considered, especially for females, because of the higher incidence of nausea and vomiting with SOX as well as high emetogenic chemotherapeutic agents (*28,29*). Sex differences in adverse reactions during SOX and CS therapies were confirmed in the G-SOX study and warrant further translational research studies to pursue the underlying cause.

Discontinued triplet therapy

The V325 study, which was mainly undertaken in European and American countries, demonstrated the superiority of triplet chemotherapy using docetaxel plus cisplatin and 5-FU (DCF) over doublet chemotherapy with cisplatin and 5-FU (CF) for patients with advanced gastric cancer (*30*). The median OS was 9.2 versus 8.6 months, and the regimen was associated with a risk reduction of 32%. The DCF regimen has not been accepted globally as a standard treatment due to its severe hematologic toxic effects (82% incidence of grade 3-4 neutropenia and 29% incidence of febrile neutropenia) and the small survival advantage.

In a randomized phase III study of Japanese patients with advanced gastric cancer known as JCOG1013 (*31*), the addition of docetaxel to cisplatin plus S-1 (DCS) was of no benefit to patients with advanced gastric cancer either for OS or PFS; the median OS was 14.2 versus

15.3 months (HR, 0.99; 95% CI 0.85-1.16; $p = 0.47$).

In a previous V325 study that revealed a survival benefit with triplet chemotherapy consisting of docetaxel, cisplatin and DCF, only 32% and 41% of patients received second-line chemotherapy in DCF and CF arms, respectively, from 1999 to 2003. However, 79% and 77% of patients received second-line chemotherapy in CS and DCS groups, respectively, in the JCOG1013 study from 2013 to 2016. It is thought that patient characteristics at baseline and during different treatment courses, including subsequent chemotherapy, between V325 and this study may be a major reason for inconsistent results. Recent phase III trials of chemotherapy versus chemotherapy plus ramucirumab, an anti-vascular endothelial growth factor receptor antibody, or pembrolizumab, an anti–programmed cell death protein 1 antibody, also did not reveal any survival benefit for biologics with regard to OS (*32-35*).

Future perspectives

Globally, capecitabine plus cisplatin has shown non-inferiority to cisplatin plus 5-FU in the treatment of advanced gastric cancer (*19*). Furthermore, oxaliplatin showed comparable activities to cisplatin in three phase III trials conducted in Europe and Japan (*20,21,22*). Thus, fluoropyrimidine plus platinum is still recognized as a standard chemotherapy worldwide. However, progress in the treatment of metastatic gastric cancer has been limited.

DNA repair systems allow cells to overcome the DNA damage induced by chemotherapy. DNA interstrand, intrastrand, and DNA–protein crosslinks caused by cisplatin are repaired by the nuclear excision repair pathway, of which excision repair cross-complementation group 1 (ERCC1) is an essential part. In the JCOG9912 trial involving patients with advanced gastric cancer, low ERCC1 expression was a significant independent favorable prognostic factor in those who received first-line chemotherapy regardless of treatment regimen (*36*). The mRNA expression of ERCC1 and dihydropyrimidine dehydrogenase in the diffuse type were higher than those in the intestinal type. Higher vascular endothelial growth factor-A expression was more commonly observed in patients with unresectable disease ($p = 0.060$), target lesions ($p = 0.052$), and liver metastasis ($p = 0.090$) (*36*). In an animal model, high ERCC1 expression led to cisplatin resistance and allowed cells to once again displace cisplatin from cellular DNA. Fluoropyrimidines can induce a variety of DNA damage in human cancer cell lines by a mechanism involving enzymes involved in DNA repair, as well as downstream factors such as p53. The expression of wild-type p53 was a strong predictor of sensitivity to 5-FU in cell lines of the National Cancer Institute's Anticancer Drug Screen panel *in vitro* (*37*). Thus, prevailing strategies used against metastatic gastric cancer need to be modified with regard to innovative treatments with current drugs and/or novel gene editing, keeping in mind each categorized population to be treated.

Conclusions

In a society of diversity including medical environment, culture, sex, comorbidities, even if the same treatment is performed, the outcome of the individual patient is different. It is important for each society to implement established treatment through clinical trials made in a similar medical circumstance like East Asia, knowing that the evidence from global trials aimed at drug approval does not necessarily show external validity. Further, individualization of treatment by reverse translational research by clinical specimens with sufficient clinical information is increasingly important in improving the treatment outcomes and QOL of individual patients.

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Road to comprehensive estimation of antimicrobial resistance (AMR) disease burden in Japan

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Abstract: Antimicrobial resistance (AMR) is currently a global health threat. Many countries have issued their own national action plans following the publication of the Global Action Plan on AMR by the World Health Organization. The government of Japan established its own National Action Plan on AMR in 2016; however, Japan's AMR countermeasures are still in the developmental stage. Recently, the AMR Clinical Reference Center (AMR CRC) in Japan estimated the disease burden of AMR in the form of number of deaths attributed to blood-stream infections caused by antimicrobial-resistant organisms. However, a more extensive and precise assessment is needed to understand the disease burden of AMR more clearly and enable us to compare these indicators with those published by other countries. Cassini and colleagues from the World Health Organization estimated the disease burden of AMR in the European Union as disability-adjusted life years (DALYs) in 2018. Their study could be considered an important milestone in terms of its thoroughness. If we hope to estimate the disease burden of AMR in a more precise manner, age-stratified patient data is needed in conjunction with a surveillance report. At present, AMR CRC is attempting to establish such data for examination at the national level – a challenging but worthwhile task.

***Keywords*:** antimicrobial resistance, DALYs, surveillance

Introduction

Antimicrobial resistance (AMR) is currently one of the greatest global health issues (*1,2*). The Japanese government published the National Action Plan on AMR in 2016 (*3*), following the publication of the Global Action Plan by the World Health Organization (WHO) (*1*). Subsequently, the AMR Clinical Reference Center (AMR CRC) was established as the main hub of AMR countermeasures in Japan in 2017 (*4*). As a part of the National Action Plan, AMR CRC has conducted epidemiological research related to this area.

Appropriate evaluation of the disease burden of AMR is needed to prepare appropriate countermeasures. The Japan Nosocomial Infections Surveillance (JANIS) program, which is organized by the Ministry of Health, Labour and Welfare, provides basic information on the incidence and prevalence of nosocomial infections and antimicrobial-resistant bacteria (*5*). The JANIS Clinical Laboratory module collects all routine microbiological test results from approximately 2,000 hospitals that voluntarily participate in the surveillance and account for a quarter of the total of approximately 8,000 hospitals across Japan. However, the disease burden of AMR is composed not only of the incidence of infections and proportion of resistance but also of other clinical and socioeconomic aspects. In this sense, surveillance data from JANIS is not tied to the individual data that have been collected to date and are thus insufficient for estimating the precise disease burden of AMR. The National Epidemiological Surveillance of Infectious Diseases Program is also a national surveillance system based on reporting from physicians and veterinarians and includes information about AMR (*6*). However, its main objective is to grasp the trends of the epidemiology of infectious diseases in accordance with the Act on the Prevention of Infectious Diseases and Medical Care; it is not designed to analyze the AMR disease burden.

Tsuzuki and colleagues estimated the disease burden of blood-stream infections (BSIs) caused by methicillin-resistant *S. aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FQREC) *via* number of deaths (*7*). However, as they stated, number of deaths is not the best proxy for the disease burden of AMR. Moreover, their results included methodological limitations due to the difficulty in correlating a surveillance report with individual clinical/socioeconomic data. Further research is required to estimate the total disease burden of AMR in Japan. In this article, we will discuss how to overcome these limitations and establish a robust and comprehensive

evaluation framework for AMR disease burden, which will enable us to understand its more precise societal impact and provide a basis for comparison with other countries.

Achievements in a previous study

There is room for discussion about what constitutes an appropriate indicator for the assessment of the comprehensive disease burden of AMR. Considering that AMR is a global health threat not limited to developed countries, disability-adjusted life years (DALYs) is one promising candidate as a single indicator of disease burden. In particular, the Global Disease Burden project has made great progress in this area and therefore supports health-care policy making (*8,9*). Cassini and colleagues from the WHO estimated the disease burden of AMR in European Union (EU) countries in the form of DALYs in 2018 (*10*). If we can estimate the disease burden of AMR in a similar way, it would constitute an important step toward AMR countermeasures in Japan because international comparisons will provide beneficial insights.

The excellence of Cassini *et al.*'s work is shown by their comprehensiveness in providing a complex of multiple research projects. First, it should be noted that the use of DALYs has been regarded as problematic in terms of its application to infectious diseases (*11*). Cassini *et al.* used DALYs values estimated by the Burden of Communicable Diseases in Europe (BCoDE) project (*12*), which was launched by the European Center for Disease Prevention and Control in 2009. The BCoDE project used a pathogen-based incidence approach to generate estimates to fully consider all chronic and long-term sequelae related to causative organisms. Their new methodology enabled them to deal with the risk of underestimation to some extent.

Cassini *et al.* used extensive data from EU countries and the European economic area (EEA) obtained from the European Antimicrobial Resistance Surveillance Network (*13*), the latter of which has provided age-stratified, country-specific data, thereby enabling users to not only compare situations among EU/EEA countries but also estimate the years of life lost (YLL) in a more appropriate manner.

Cassini *et al.* also evaluated years lost due to disability (YLD) in a detailed manner. Their evaluation of YLD is based on another article published in 2018 based on the results of the BCoDE project (*14*). They included not only disability attributed to infectious diseases but also length of stay (LOS) in hospitals due to infectious diseases in the context of YLD. For example, they calculated disability from BSIs and multiplied that by mean LOS of BSIs. By using this method, the burden of AMR can be seen more clearly because LOS attributed to infectious diseases caused by antimicrobial resistant organisms tends to be longer. Additionally, Colzani and colleagues developed a new freely available toolkit for DALYs calculation in the BCoDE project (*15*). This toolkit made their disease models openly accessible to everyone, even from outside EU/EEA countries.

Limitation of the current evidence from Japan

As mentioned above, AMR CRC published the first evidence on the disease burden of AMR in Japan last December (*7*). That work can be appreciated because it provides indicators for Japanese healthcare policy makers. Nevertheless, its limitations should be considered and further evaluation is required to fully understand the disease burden of AMR in Japan.

The limitations of our work can be observed more clearly when we consider differences between our work and that of Cassini *et al.*. Our work focused on the number of deaths attributable to BSIs caused by MRSA and FQREC. These two strains account for the largest part of the disease burden of AMR and BSIs are the main cause of death due to infectious diseases. Nevertheless, this work does not explain the "total" disease burden of AMR because it does not include diseases other than BSIs, clinical outcomes other than death, and organisms other than MRSA and FQREC.

In addition, we should take note that several methodological challenges have not yet been resolved. We estimated the number of deaths due to BSIs in a similar way to Cassini *et al.*. We used the case fatality ratio derived mainly from two domestic studies (*16,17*). However, these studies are largely based on a cohort of tertiary care hospitals; therefore, it is difficult to reflect heterogeneity among different level facilities. In Japan, it is generally difficult to find evidence on the epidemiology of infectious diseases such as mortality from BSIs. Furthermore, we could not find any data on the prevalence of sequelae caused by infectious diseases, LOS due to AMR, and so forth.

Future challenges

As explained above, evaluation of disease burden brought about by AMR needs to be more precise and comprehensive. However, there is a large gap between our ideals and reality. We will have to bridge this gap within the next few years. Many types of data and evidence will be necessary to construct our own framework for evaluating AMR disease burden. The list of required data and evidence is as follows:

i) Age-, disease-, and organism-specific incidence, mortality, and morbidity (*e.g.*, incidence of MRSA pneumonia in infants, mortality of FQREC BSIs in elderly, *etc.*);

ii) Age-, disease-, and organism-specific LOS (LOS of MRSA BSIs, *etc.*);

iii) Disability weight of infectious diseases

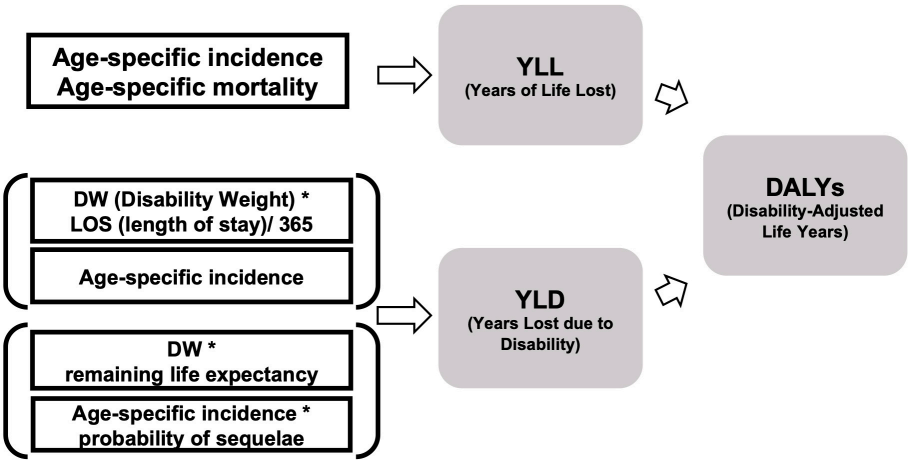

Figure 1. A flowchart regarding the processes in which required data and evidence turn into indicators of disease burden.

(pneumonia, BSIs, *etc.*);

iv) Disability weight of sequelae due to infectious diseases (cognitive impairment, physical impairment, *etc.*).

A flowchart regarding the processes in which required data and evidence turn into indicators of disease burden is presented in Figure 1.

DALYs are represented as the sum of YLL and YLD, so age-specific incidence and mortality data are used to calculate YLL. One of the strengths of the previous study by Cassini *et al.* is their elaborate review process of mortality estimation (*10*). Ideally, we would also combine results of multiple studies to reflect on the uncertainty and heterogeneity of probabilities such as mortality. The same can be said of morbidity when estimating the burden of sequelae.

It is noteworthy that LOS in Japanese healthcare facilities seems to be longer than that in other developed countries. For example, Muramatsu and Liang reported that the average LOS in Japan was 2.8 times longer than that in the United States (*18*). Although the recommended duration of treatment is usually defined among infectious diseases, it is merely a guide and it is possible that LOS in Japan is indeed longer than in other countries; therefore, domestic data is desirable if we hope to estimate more appropriate YLD.

Establishing our own value for disability weight is desirable because quality of life will be different among people in different situations even if they have the same disease or disability (*19-21*).

At present, we are preparing for what must be done. JANIS recently published age-specific AMR incidence levels. AMC CRC established the AMR One Health Platform, which offers age and specimen stratified AMR data at the national level (*22*). The national receipt database Open Data Japan (*23*) provides individual health insurance claim data, which might enable exploration of the prevalence of sequelae caused by infectious diseases.

Much work remains in terms of epidemiological evidence. One of our aims is to encourage Japanese clinicians and epidemiologists to conduct novel research projects that reveal the actual mortality and LOS due to AMR, and hopefully involve different levels of facilities (primary, secondary, and tertiary).

Finally, we should not forget that Cassini *et al.* are also halfway toward realizing a more precise, comprehensive evaluation of AMR disease burden. For instance, among their stated limitations, they neither considered age-specific mortality when they calculated YLL nor statistical methods in their review process of previous studies (*10*). If we could include YLL calculated by age-specific mortality and estimate mortality with robust statistical methods, it would be invaluable for our future research. In addition, the research group has not yet attempted to estimate the economic impact of AMR. Clearly, longer LOS and higher treatment costs due to AMR may be considered as an economic burden on our society. If we could conduct cost-effectiveness or cost-benefit analysis of AMR at the national level, the results would be of notable value for health policy decision makers.

As described above, we currently face many challenges on our way to realizing a more precise and comprehensive evaluation of AMR disease burden. Although they are difficult to deal with, it is worth tackling them simultaneously because reliable indicators of AMR are needed for health policy making in Japan. We have already been putting forth more effort and believe that we will overcome these challenges in the near future.

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General patients' expectations on online accessibility to their electronic health records in Japan

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Abstract: Allowing patients to access their electronic health records (EHR) online, that we call the patient open-EHR, may help patients better understand and remember their health information, leading to improved health outcomes. In Japan, such solution is not yet widespread, and general patients' expectations for such solution are not known. The OpenNotes initiative in the United States of America (USA) had done various studies concerning the intervention of sharing doctors' notes, which are part of the EHR, with patients. Our study objective is to explore general patients' expectations toward potential benefits and risks of the patient open-EHR solution if given chance to use in Japan. A cross-sectional study was done using an online questionnaire. One hundred and eighty-three general patients without previous experience using the patient open-EHR service, responded to our survey after being recruited through SNS and posters at a university hospital not offering the solution. Comparison with the result of the OpenNotes original study, conducted in a similar setting, was also done. The results showed that participants were, similarly to the OpenNotes results, positive about the system's potential benefits; 90% agreed on the system ability to help them better understand their condition and remember their healthcare plan. On the other hand, they were much concerned about the potential risks especially privacy; 62% agreed they would be worried about their privacy. Adequate measures to provide highly secured systems and to allow patients to be better informed about the use of their personal health records should be taken to comfort future users.

***Keywords*:** EHR, patient understanding, remembering, OpenNotes, privacy concern

Introduction

Healthcare Information Technology (HIT) is changing how the healthcare industry operates globally and has already begun to reduce waste and help improve health outcomes (*1*). Electronic health records (EHR) are major components of HIT. The use of EHR has the potential to facilitate patient access to personal records, test results, health education tools, and tools for tracking and assessing the progress of chronic disease management. In other countries, the impact of sharing electronic medical and health records with patients on different aspects of quality and safety of care was previously studied (*2-6*). A systematic review showed that patient online access to EHR and linked services offer increased convenience and satisfaction (*4*). However, health professionals were concerned about impact on workload and risk to privacy. Another systematic review article suggested that there was insufficient evidence about the effect of patient accessible EHRs on health outcomes for patients (*5*). Recently, new possibilities have arisen from innovative studies that enabled patients to read their physician notes, which are part of the EHR, online after the clinical encounter. The OpenNotes initiative had shown positive results concerning sharing doctors' notes with patients (*7-9*). After reviewing their visit notes, patients reported better understanding and remembering and feeling more in control of their care (*9*).

Many movements have started in Japan, about 20 years ago, to help and promote the sharing of EHR data between hospitals or medical institutions in the same region (*10*). Some of these regional networks allow the sharing of EHR data with patients online. However, the number of registered patients nationwide is still very low. Based on survey done by the Japan Medical Association Research Institute (JMARI) on these regional networks in March 2016, approximately 250 regional EHR networks are assumed to have existed nationwide and the number of registered patients at 154 of these networks was less than 1.2 million (*11,12*). Out of these registered 1.2 million approximately 700,000 patients only get access to their EHR data.

In Japan, to the best of the authors' knowledge, there is limited research regarding the sharing of electronic medical and health records with patients (*13,14*). A previous study on attitudes towards releasing medical information to patients with focus on ethical issues was done (*13*), which demonstrated that information raising

ethical issues (*i.e.* child abuse) strongly influences the judgment of whether to release the records to patients or not. Another study focused on pregnant women's electronic medical records (EMR)-related needs (*14*). It showed that pregnant Japanese women want accessible and exchangeable EMRs with explanations and summaries.

The objective of the present study is to explore general patients' expectations toward potential benefits or risks of the patient open-EHR solution if given chance to use in Japan. Besides this, we investigated the relationship between respondents' characteristics and their views and also compared our results with those of the OpenNotes study before having doctors' notes shared with patients (*8*).

Materials and Methods

Overall design

A cross-sectional study was done using an online questionnaire. The questionnaire we used was based on the survey done by the OpenNotes initiative original study conducted before having doctors' notes open to patients (*8*). The questionnaire was prepared in both the English and Japanese languages. The one in English was to provide further convenience for foreign-origin residents in Japan, who are more familiar using English than Japanese. Questionnaires were conducted online by using SurveyMonkey. Respondents could skip individual questions or exit at any point. Responses up to the point of exit were used in the data analysis. Questionnaires were designed to take less than 20 minutes. No incentives were given to the respondents. The institutional review board of Teikyo University approved the overall project plan (Approval ID: TUIC-COI 18-0851).

Participants

Participants were recruited through the internet social networks (Facebook, LINE, mailing lists) and also at the Teikyo University Hospital that is not providing patient open-EHR service, by displaying a poster that invited patients to participate in the survey. Individuals 18 years old and older living in Japan who had previously accessed Japanese hospitals/clinics in the last one year were invited to participate. The first recruitment through social networks was done in November 2018 and through posters in the Teikyo University Hospital in April 2019. Answers collected until October 2019 were used in the analysis.

Measurements

Participants views on potential benefits (better understanding, remembering and others) and risks (privacy concern and others) of the patient open-EHR were investigated. Our key research questions asked about participants' views on the statements listed in Table 1. For statements 2-9 the question was "Imagine what it might be like to read your EHR online. If you could access your EHR online, would you agree or disagree with the statements below?". Participants could respond to each item on a five-point Likert scale, where the response choices ranged from "strongly disagree" to "strongly agree". Short expressions in Table 1 would be used when summarizing the results in later part of this paper. The following socio-demographic data were collected: age, gender, nationality, educational level, occupation, household income, satisfaction with present life, people living with, internet access tool, overall health status, previous diagnosis/treatment. The following items were also evaluated using already validated scales' questions as follow: *i*) patient preference for decision making (DM), measured using decision making preference scale (*15*); *ii*) health literacy (HL), measured using communicative and critical HL score (*16*); *iii*) patient trust in physician, measured using trust in physician score (*17*); and *iv*) patient ability to ask/understand/remember, using ask understand remember assessment (AURA) score (*18*).

Statistical analysis

For patient characteristics, categorical variables were presented as proportions, and continuous variables

Table 1. Key statements used in the survey

		Statement	Short expression
Potential benefits	1	In general, making EHR accessible to patients on a secure Internet website or application is a good idea.	Good idea
	2	I would better understand my health and medical conditions.	Understand
	3	I would better remember the plan for my care.	Remember
	4	I would take better care of myself.	Self-care
	5	I would be more likely to take my medications as prescribed.	Take medication
	6	I would feel more in control of my health care.	In control
	7	I would be better prepared for visits.	Prepared
Potential risks	8	I would worry more.	Worry
	9	I would be concerned about my privacy.	Privacy
	10	The EHR would be more confusing than helpful.	Confusing

EHR, electronic health record.

were summarized with means and standard deviations or medians. Statements on potential benefits and risks were answered using a 5-level agree-disagree response set. The responses were dichotomized into agree category that combined the "agree" and "strongly agree" responses, and the other category that combined other responses. We examined the relationship between patient responses, on the benefits and risks of patient open-EHR, and patient characteristics, such as sex, age, education, health status, preference for decision making, health literacy and patient trust in physician. The chi-square test was used to examine the relationship between patient background information and the proportion of agree on the benefits or risks of the patient open-EHR with a significant level of 0.05 for a two-sided test. Statistical analysis software used was SAS 9.4. Comparison with the OpenNotes results was done using age-adjusted agree proportions on potential benefits and risks. Age was chosen because age was related to the agree proportions about potential benefits and because distributions of age were different in the two populations (the current study and the OpenNotes study).

Results

One hundred and sixty-six participants accessed the Japanese survey link and 70 the English survey link. Out of these respondents, 5 in the Japanese and 6 in the English previously used patient open-EHR service. From the remaining non-user respondents, we got 138 completed answers to our analysis questions in the Japanese survey and 45 completed answers in the English survey, making a total number of non-user respondents equal to 183.

Respondents' characteristics and their views regarding the potential benefits/risks results were shown in Table 2 and Table 3. The mean age of respondents was 41 years old. Attitudes of non-user respondents met our expectations; Most of respondents (86%) were positive about the prospect of accessing freely their medical records online, regardless of demographics or health and other characteristics. 90% agreed that the patient open-EHR would help them understand their health condition and remember their health plan. On the other hand, regarding worries on potential risks, we found a relatively high proportion worried on potential risks, especially privacy (62%) (Table 3).

Tables 4-6 show results on the relationship between the agree proportion on some of the potential benefits (Understand and Remember) and risks (Privacy) of the patient open-EHR, and the patients characteristics listed below; sex, age, education, overall health, preference for decision making, health literacy and patient trust in physician. Only the relationship between age and agree proportion on Understand statement that was statistically significant (p = 0.012) (Table 4). The agree proportion on Understand was low for respondents aged 50 and above and also for young category aged 18-29.

We also compared our results with ones of the OpenNotes study (*8*) (Table 7). We chose to compare with the results of the patients from the adult medicine and HIV clinics at Harborview Medical Center (HMC) because this center did not have patient online portals at the beginning of the original study (*8*). In terms of demographic characteristics and self-reported health status of HMC patients, the mean age of participants was 49 years old, 24% of participants were women, 73% were with college degree and above and 27% self-

Table 2. Non-user respondents' characteristics (n = 183)

Characteristic	Numerical value
Age, *n* (%)	
18-29	19 (10)
30-39	66 (36)
40-49	73 (40)
50-59	19 (10)
60-69	3 (2)
70 and above	3 (2)
Female, *n* (%)	127 (69)
Education, *n* (%)	
Elementary or junior high school	0 (0)
High school	6 (3)
Some college or 2-year degree	21 (12)
4-year university graduate	79 (43)
Graduate school	77 (42)
Overall health, *n* (%)	
Good	62 (34)
Fairly good	87 (47)
Fair	23 (13)
Fairly poor	10 (5)
Poor	1 (1)
Smartphone users, *n* (%)	171 (93)
Decision making preference score	
Mean (SD)	13.5 (3.4)
Median	14
Communicative and critical HL score	
Mean (SD)	17.9 (3.6)
Median	18
Trust in physician score	
Mean (SD)	15.7 (2.7)
Median	16
AURA score	
Mean (SD)	12.7 (2.3)
Median	12

SD, standard deviation; HL, health literacy; AURA, ask understand remember assessment.

Table 3. Agree proportion of non-user respondents about the potential benefits/risks (n = 183)

Statement (short expression)		*n* (%)
Potential benefits	Good Idea	157 (86)
	Understand	165 (90)
	Remember	164 (90)
	Self-care	134 (73)
	Take medication	109 (60)
	In control	135 (74)
	Prepared	143 (78)
Potential risks	Worry	61 (33)
	Privacy	113 (62)
	Confusing	49 (27)

Table 4. Relationship between the agree proportion of non-user respondents about the statement regarding Understand and respondents' characteristics (*n* = 183)

Characteristic	Total *n*	Agree *n* (%)	*p* value
Sex			0.417
Male	56	52 (93)	
Female	127	113 (89)	
Age			0.012
18-29	19	15 (79)	
30-39	66	62 (94)	
40-49	73	69 (95)	
50 and above	25	19 (76)	
Education			0.267
Up to 2years college degree	27	25 (93)	
4-year university graduate	79	68 (86)	
Graduate school	77	72 (94)	
Overall health			0.628
Good/ Fairly good	149	135 (91)	
Fair	23	21 (91)	
Poor/ Fairly poor	11	9 (82)	
Decision making preference score			0.234
Low (< 10)	22	20 (91)	
Moderate (10 AND ≤ 16)	127	117 (92)	
High (> 16)	34	28 (82)	
Communicative and critical HL score			0.453
Low (< 15)	32	30 (94)	
High (≥15)	151	135 (89)	
Trust in physician score			0.561
Low (< 15)	60	53 (88)	
High (≥ 15)	123	112 (91)	

HL, health literacy.

Table 5. Relationship between the agree proportion of non-user respondents about the statement regarding Remember and respondents' characteristics (*n* = 183)

Characteristic	Total *n*	Agree *n* (%)	*p* value
Sex			0.669
Male	56	51 (91)	
Female	127	113 (89)	
Age			0.481
18-29	19	17 (90)	
30-39	66	62 (94)	
40-49	73	64 (88)	
50 and above	25	21 (84)	
Education			0.990
Up to 2years college degree	27	24 (89)	
4-year university graduate	79	71 (90)	
Graduate school	77	69 (90)	
Overall health			0.580
Good/Fairly good	149	132 (89)	
Fair	23	22 (96)	
Poor/Fairly poor	11	10 (91)	
Decision making preference score			0.512
Low (< 10)	22	19 (86)	
Moderate (10 AND ≤ 16)	127	116 (91)	
High (> 16)	34	29 (85)	
Communicative and critical HL score			0.399
Low (< 15)	32	30 (94)	
High (≥ 15)	151	134 (89)	
Trust in physician score			0.691
Low (< 15)	60	53 (88)	
High (≥ 15)	123	111 (90)	

HL, health literacy.

Table 6. Relationship between the agree proportion of non-user respondents about the statement regarding Privacy and respondents' characteristics (*n* = 183)

Characteristic	Total *n*	Agree *n* (%)	*p* value
Sex			0.890
Male	56	35 (63)	
Female	127	78 (61)	
Age			0.063
18-29	19	15 (79)	
30-39	66	46 (70)	
40-49	73	39 (53)	
50 and above	25	13 (52)	
Education			0.959
Up to 2years college degree	27	16 (59)	
4-year university graduate	79	49 (62)	
Graduate school	77	48 (62)	
Overall health			0.988
Good/Fairly good	149	92 (62)	
Fair	23	14 (61)	
Poor/Fairly poor	11	7 (64)	
Decision making preference score			0.453
Low (< 10)	22	15 (68	
Moderate (10 AND ≤ 16)	127	80 (63)	
High (> 16)	34	18 (53)	
Communicative and critical HL score			0.923
Low (< 15)	32	20 (63)	
High (≥ 15)	151	93 (62)	
Trust in physician score			0.507
Low (< 15)	60	35 (58)	
High (≥ 15)	123	78 (63)	

HL, health literacy.

Table 7. Comparison of age-adjusted agree proportion about the potential benefits/risks with the OpenNotes results (*8*)

Statement	Non-users in Japan *n* = 183 (%)	OpenNotes *n* = 272 (%)
Potential benefits		
Good idea	162 (89)	264 (97)
Understand	154 (84)	256 (94)
Remember	159 (87)	256 (94)
Self-care	129 (71)	231 (85)
Take medication	103 (57)	193 (71)
In control	111 (61)	261 (96)
Prepared	137 (75)	248 (91)
Potential risks		
Worry	46 (25)	35 (13)
Privacy	103 (56)	95 (35)
Confusing	41 (22)	38 (14)

reported fair or poor health status. Our survey results on respondents' views were represented using age-adjusted proportions. Despite the differences in proportions' values shown in Table 7, we found a similar trend in both groups; positiveness about the potential benefits and some worries about the potential risks, from which worries on privacy were not negligible for both groups.

Discussion

The present results met our expectations; similarly to

the US, most respondents to our survey in Japan were positive about the prospect of accessing freely their EHR online. Most agreed that this access could help improving their understanding of health and medical condition and remembering the care plan (Table 3). This suggests that the EHR could be used not only to share information between hospitals but also with patients. Such solution could contribute to further enhancing the efficiency of the communication between doctor and patient by improving patient's understanding and remembering of information received during the consultation.

In our results, the percentage of 'Agree' on Understand statement varied by age group. A smaller proportion of old participants aged 50 and above agreed on Understand statement (Table 4). This might be because older people could be still reluctant to ICT solutions. Therefore, this category of patients might need to try first in order to get convinced about the benefits of such solution. The proportion in young category aged 18-29 was slightly low as well (Table 4), this could be because younger subjects generally do not feel difficulty in understanding their health and medical conditions due to their limited experiences in complicated conditions.

Worries on potential risks especially privacy were not negligible independently of patients' characteristics (Table 3 and Table 6). In order to comfort future users, it will be required to provide highly secured systems that allow the protection of private health information and to explain to patients the measures taken. Moreover, many patients might still not feel comfortable with the idea that hospitals would disclose their private health information to other hospitals without knowing exactly what data are disclosed. Giving access to patients through the patient open-EHR and giving them the right to see and select exactly the data to share with other hospitals might help in further comforting patients about their privacy since they would feel in control of what happens to own health data.

Privacy worries are common with the US and other countries in Europe as well. In order to address such worries, the European Union adopted in 2016 a new regulation on the protection of personal data, also known as the EU General Data Protection Regulation (GDPR). This regulation provides more rights to citizens to be better informed about the use of their personal data and gives clearer responsibilities to people and entities using personal data (*19*). Clear and simplified guides were published to inform patients on their rights (*20*). In the US, the Department of Health & Human Services (HSS), based on the requirement of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), had developed and published the HIPAA Privacy Rule and the HIPAA Security Rule in order to protect the privacy and security of certain health information. The Privacy rule states clearly the rights each patient has over own health information (whether electronic, written, or oral) and sets rules and limits on who can look at and receive this health information (*21*). In order to help patients easily understand their rights, a series of short, educational videos were also developed and published in the HSS homepage (*21*).

In Japan, the Ministry of Health Labor and Welfare (MHLW) has also developed regulations and guidelines regarding the security management of health information systems (*22*). Regarding Privacy, the MHLW has also set guidelines for appropriate handling of personal information by medical and nursing care providers (*23*). However, to the authors' knowledge no clear information targeting patients themselves to inform them about their rights was published so far by the regulators in Japan. Increased worries regarding privacy as shown in our survey results (Table 3 and Table 6) could be explained by the lack of clear information on patients' rights regarding their electronic health records. Providing clear and easily understandable information to patients of different categories is needed in Japan.

Our study has some limitations. First, our survey was conducted online and results may not represent the overall population. However, since the solution is ICT based, we expect its future users will be similar to the respondents of this survey, who are familiar with computers and the internet. Second, we did not perform testing to evaluate reliability or validity of the questions that were taken from the questionnaire used in the OpenNotes study. However, after translation we did multi-check and testing with a small group before launching the survey.

In conclusion, needs and high expectations regarding the patient open-EHR solution were visualized through our study targeting non-user general patients in Japan. Such solution could bring benefits toward improving doctor-patient communication efficiency and patient satisfaction. The concern on privacy is a major barrier that should be addressed in order to comfort and encourage future users of the solution. Clear information targeting patients on their rights regarding their electronic health information should be made public as well. On the other hand, doctors' attitudes toward such solution should be also addressed in future studies.

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BRIEF REPORT
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COVID-19 can suddenly become severe: a case series from Tokyo, Japan

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Abstract: Since the initial report of coronavirus disease (COVID-19) from the City of Wuhan, China in December 2019, there have been multiple cases globally. Reported here are 11 cases of COVID-19 at this hospital; all of the patients in question presented with relative bradycardia. The severity of the disease was classified into four grades. Of the patients studied, 3 with mild COVID-19 and 3 with moderate COVID-19 improved spontaneously. Lopinavir/ritonavir was administered to 3 patients with severe COVID-19 and 2 with critical COVID-19. Both patients with critical COVID-19 required mechanical ventilation and extracorporeal membrane oxygenation. Both patients with critical COVID-19 had a higher fever that persisted for longer than patients with milder COVID-19. The respiratory status of patients with critical COVID-19 worsened rapidly 7 days after the onset of symptoms. Relative bradycardia may be useful in distinguishing between COVID-19 and bacterial community-acquired pneumonia. In patients who have had a fever for > 7 days, the condition might worsen suddenly.

***Keywords*:** COVID-19, SARS-CoV-2, pneumonia

Introduction

Since the initial reports of coronavirus disease (COVID-19) infection from the City of Wuhan, China in December 2019, there have been multiple cases globally. As of May 1, 2020, there were 3,175,207 confirmed cases worldwide. Japan has reported 14,545 cases, and the number continues to increase.

The mortality rate of COVID-19 is reported to be 2.3% (*1*). The number of severe cases will increase as the number of patients who contract the disease increases. At present, most case reports are from China, and there is a lack of detailed reports from Japan. A better understanding of the clinical profile will help improve the treatment and prevention of COVID-19.

The aim of this report was to describe the clinical characteristics of 11 patients with COVID-19 at this hospital.

Patients and Methods

This study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM) (approval no. NCGM-G-003472-02) and conducted in accordance with the Declaration of Helsinki. Patient information was anonymized and de-identified prior to analysis. Because of the retrospective nature of the study, the requirement for patient consent was waived.

A retrospective cohort study of patients with COVID-19 was conducted between January 2020 and February 2020 at the NCGM, Tokyo, Japan. This center has approximately 780 hospital beds. All patients were admitted through the NCGM referral center for infectious disease from January 26, 2020 to February 13, 2020.

The following information was collected from the patient charts: *i*) characteristics and comorbidities; *ii*) symptoms, body temperature, heart rate, oxygen demand, treatment, and use of a respirator and extracorporeal membrane oxygenation (ECMO); and *iii*) 30-day mortality.

The severity of COVID-19 was classified into 4 grades. Upper respiratory symptoms without

pneumonia were graded as mild. Pneumonia requiring no supplemental oxygen was graded as moderate, whereas the requirement for supplemental oxygen was graded as severe. The requirement for intensive care, including mechanical ventilation, was graded as critical. A body temperature > 37.5°C was defined as a "fever". "Abatement of a fever" was defined as the absence of a fever for > 48 h. The "duration of fever" was calculated as the day when the body temperature first reached ≥ 37.5°C to the day when the body temperature finally dropped to ≤ 37.5°C. "Relative bradycardia" was determined based on the definition of Cunha *et al*. (*2*). Given the difference between axillary temperature and oral temperature, body temperature was calculated by adding 0.3°C (0.5°F) to the axillary temperature (*3*). The values of continuous variables are expressed as the median and range.

Results and Discussion

A total of 11 patients with COVID-19 were examined in this study. Median (range) age was 54 years (28-83), and 4 patients (36.4%) were female. One patient (9.1%) had diabetes mellitus, 1 (9.1%) had prostate cancer, 1 (9.1%) had bradycardia, 1 (9.1%) had Alzheimer's dementia, and no patients had pulmonary disease (Table 1).

The most common symptom among all of the patients was a fever (9 patients, 81.8%), followed by a sore throat (4 patients, 36.4%), cough (4 patients, 36.4%), and dyspnea (4 patients, 36.4%). The median duration of fever (range) was 6 days (0-31), and the 30-day mortality was 1 (9.1%) (Table 2). The relationship between body temperature and pulse is shown in Figure 1. Relative bradycardia was confirmed in almost all of the patients.

Patients were categorized into 4 groups: *i*) 3 with mild COVID-19; *ii*) 3 with moderate COVID-19; *iii*) 3 with severe COVID-19, and *iv*) 2 with critical COVID-19. All 5 of the patients with severe or critical COVID-19 received lopinavir/ritonavir (LPV/r). The 2 patients with critical COVID-19 both required mechanical ventilation as well as ECMO. Patients with

Table 1. Characteristics of patients with COVID-19

Items	Mild, *n* = 3	Moderate, *n* = 3	Severe, *n* = 3	Critical, *n* = 2
Age (range)	64 (28-70)	52 (41-54)	50 (33-83)	78.5 (74-83)
Female (%)	2 (66.7)	0 (0)	2 (66.7)	0 (0)
BMI (range)	27.2 (23.0-28.5)	23.5 (21.8-24.7)	25.5 (23.3-25.7)	25.2 (24.8-25.6)
Comorbidity				
Pulmonary disease (%)	0 (0)	0 (0)	0 (0)	0 (0)
Neurologic disease (%)	1 (33.3)	0 (0)	0 (0)	0 (0)
Cardiovascular disease (%)	0 (0)	0 (0)	0 (0)	1 (50.0)
Malignancy (%)	1 (33.3)	0 (0)	0 (0)	0 (0)
Diabetes (%)	0 (0)	0 (0)	0 (0)	1 (50.0)

Table 2. Symptoms, treatment, and outcomes for patients with COVID-19

Items	Mild, *n* = 3	Moderate, *n* = 3	Severe, *n* = 3	Critical, *n* = 2	Total, *n* = 11
Symptom					
Fever (%)	2 (66.7)	3 (100)	2 (66.7)	2 (100)	9 (81,8)
Sore throat (%)	0 (0)	2 (66.7)	2 (66.7)	0 (0)	4 (36.4)
Cough (%)	0 (0)	1 (33.3)	2 (66.7)	1 (50)	4 (36.4)
Dyspnea (%)	0 (0)	1 (33.3)	1 (33.3)	2 (100)	4 (36.4)
Runny nose (%)	1 (33.3)	1 (33.3)	0 (0)	1 (50)	3 (27.3)
Phlegm (%)	0 (0)	0 (0)	2 (66.7)	1 (50)	3 (27.3)
Nausea (%)	0 (0)	1 (33.3)	1 (33.3)	1 (50)	3 (27.3)
Malaise (%)	0 (0)	1 (33.3)	1 (33.3)	1 (50)	3 (27.3)
Headache (%)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (9.1)
Chills (%)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (9.1)
Diarrhea (%)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (9.1)
Abdominal bloating (%)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (9.1)
Treatment					
Oxygen (%)	0 (0)	0 (0)	3 (100)	2 (100)	5 (45.5)
LPV/r (%)	0 (0)	0 (0)	3 (100)	2 (100)	5 (45.5)
Mechanical ventilation (%)	0 (0)	0 (0)	0 (0)	2 (100)	2 (18.2)
ECMO (%)	0 (0)	0 (0)	0 (0)	2 (100)	2 (18.2)
Steroid (%)	0 (0)	0 (0)	1 (33.3)	2 (100)	3 (27.3)
Interferon α2a (%)	0 (0)	0 (0)	0 (0)	1 (50)	1 (9.1)
Duration of fever (range)	2 (0-5)	6 (1-12)	6 (6-19)	23.5 (16-31)	6 (0-31)
30-day mortality	0 (0)	0 (0)	0 (0)	1 (50)	1 (9.1)

LPV/r, lopinavir/ritonavir; ECMO, extracorporeal membrane oxygenation.

critical COVID-19 tended to have a fever for a longer period than patients with less severe COVID-19 (23.5 days [16-31] *vs*. 6 days [0-19]). Patients with critical COVID-19 presented with a higher body temperature than patients with mild-severe COVID-19 (39.0°C [38.4-39.8°C] *vs*. 37.1°C [36.0-38.7°C]). Progress charts for patients with critical COVID-19 are shown in Figure 2. In both cases, respiratory status deteriorated rapidly on days 9-10, and the patient had to be intubated.

Based on an analysis of 11 patients with COVID-19, an important finding is that almost all of the patients exhibited relative bradycardia. According to Cunha *et al*., relative bradycardia is a finding reported in intracellular parasite infections, such as typhoid fever and mycoplasma pneumonia, and viral diseases, such as dengue fever. Since COVID-19 is also a viral disease caused by the severe acute respiratory syndrome coronavirus 2, detection of relative bradycardia is not surprising (*2*). Relative bradycardia may be useful in distinguishing COVID-19 from bacterial community-acquired pneumonia.

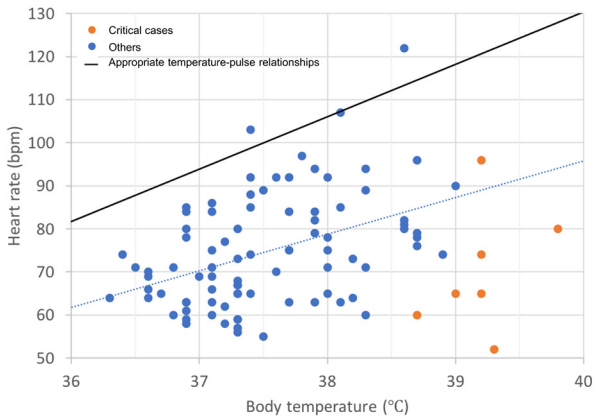

Figure 1. Scatter plot of heart rate and body temperature for all patients. All of the patients with COVID-19 displayed relative bradycardia. Patients with critical COVID-19 tended to have a higher fever than those with less severe COVID-19.

COVID-19 has a wide range of clinical presentation, from asymptomatic or mildly symptomatic patients to those requiring intensive care (*4,5*). The current study classified the severity of the disease into 4 grades. COVID-19 needed to be classified into 4 grades of severity and different treatment plans needed to be devised for each. In patients with mild to severe COVID-19, fever resolved within 7 days, whereas in patients with critical COVID-19, respiratory status deteriorated rapidly after day 7, and a ventilator was needed. Patients with critical COVID-19 had a markedly higher body temperature than patients with less severe COVID-19 (Figure 2). This finding is consistent with a previous study reporting that the period from onset to development of acute respiratory distress syndrome takes approximately 8 days (*6*). According to a study by Pan *et al*., computed tomography (CT) scans revealed the most deterioration on day 10 after the onset of COVID-19 (*6*). Risk factors for mortality include being elderly, a decreased lymphocyte count, X-ray findings of diffuse patchy/interstitial lung opacities, and comorbidities, such as heart disease, diabetes mellitus, chronic lung disease, hypertension, or malignancy, high SOFA score, and high d-dimer (*6-8*). The condition of patients with risk factors for mortality and a fever for > 7 days may worsen suddenly. Therefore, strict monitoring and a prompt transition to supportive care, such as mechanical ventilation or ECMO, are required.

The current study had several limitations. First, it only included 11 patients for the sake of time. Nonetheless, the number of patients with COVID-19 is increasing daily, and additional cases will need to be studied in the future. Second, this was a retrospective study, and treatment strategies varied. All of the patients with severe or critical COVID-19 received LPV/r, but some patients also received steroids and interferon alpha. These differences may have affected the severity of the disease. A prospective study needs to

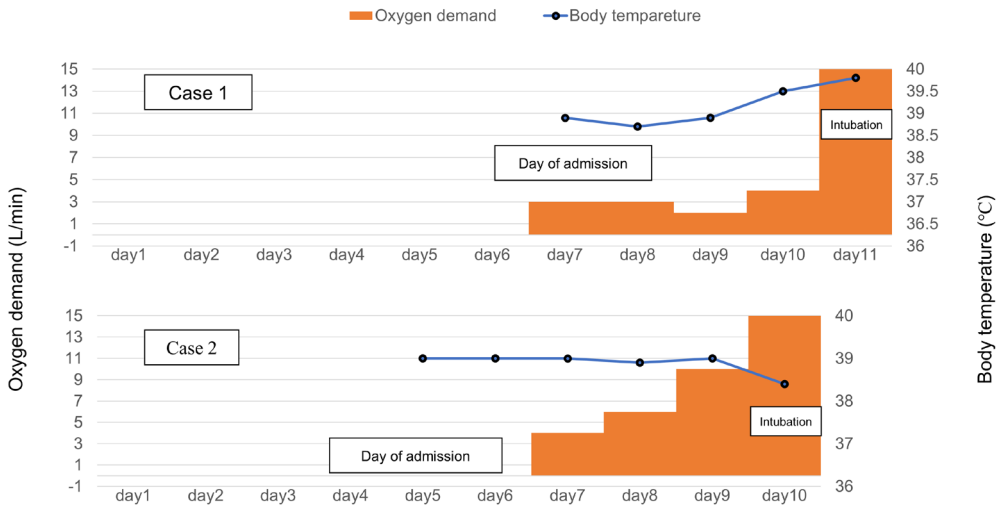

Figure 2. Progress charts for patients with critical COVID-19. Shown here are progress charts for 2 patients with critical COVID-19. They had a high fever for over 7 days and their respiratory status rapidly deteriorated.

be conducted in the future.

In conclusion, relative bradycardia may be useful in distinguishing COVID-19 from bacterial community-acquired pneumonia. COVID-19 can be classified into 4 grades of severity. The condition of patients presenting with a fever for > 7 days may worsen suddenly.

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Metabolic changes of Japanese schizophrenic patients transferred from hospitalization to outpatients

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Abstract: It is well known that schizophrenic patients have high incidence of metabolic syndrome and life-style related diseases. There are reports that the rates of these diseases are increased more in outpatients than inpatients, but are also reports that the rates are not different between both patient groups. These differences might be related to the length of hospitalization. Hospitalization of Japanese psychiatric patients is about 300 days, much longer than western countries (below 50 days). Therefore, we investigated lipid and glucose metabolism of schizophrenic patients transferred from hospitalization to outpatients at Kohnodai hospital with a mean of 80 days hospitalization period to clarify metabolic characteristics in Japanese patients. Study participants were 144 schizophrenia inpatients and 109 outpatients at Kohnodai Hospital. These 109 outpatients were followed for approximately 2 years, without changes of administrated drugs, and from 144 inpatients. Data from outpatients were obtained at 6 months, 1 year and 2 years after their discharge. Outpatients 2 years after discharge had significantly higher levels of total cholesterol, triglyceride and non-high density lipoprotein (non-HDL) cholesterol than inpatients, accompanied with an increase of body weight. Serum HDL-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels had no significant difference between both groups. These lipids and glucose levels also showed the same tendency in outpatients 0.5 year and 1 year after discharge as those after 2 years. We found that schizophrenic patients in our study appeared to have changes of lipid metabolism 2 years after their discharge, but no significant changes of glucose metabolism, such as FPG and HbA1c.

***Keywords*:** schizophrenia, inpatients, glucose metabolism, lipid metabolism, outpatients

Introduction

There are many reports of increased death rate and short life expectancy in psychiatric patients (*1,2*). It is reported that atherosclerotic diseases play an important role in their cause of death (*3,4*). Schizophrenic patients are shown to have an increased ratio of life-style related diseases such as, hypertension, diabetes, dyslipidemia and so on (*5,6*). They also have a tendency towards unhealthy lifestyles, which are shortness of exercise, inappropriate diet customs, and increased smoking rates (*7*). These lifestyles are thought to be one of the causes of developing atherosclerosis.

Meta-analysis of prevalence of metabolic syndrome and metabolic abnormalities of schizophrenia by Mitchell *et al.* (*8*) showed that the rates of metabolic syndrome had minor differences in countries (the United States (32.5%), Finland (34.5%), Spain (30.2%) and Turkey (30.1%)), but had almost no differences between outpatients (31.8%) and inpatients (30.4%), and males (34.8%) and females (34.8%). It was also reported that the rates of the diagnosis of diabetes among schizophrenia patients were similar in either outpatients or inpatients, and were approximately 2 times compared with the rates of diabetes among controls (*9*).

Sugawara *et al.* and Sugai *et al.* (*10,11*) investigated in Japan the incidence of metabolic syndrome, obesity, hypertension, diabetes and dyslipidemia in schizophrenic patients. There have been few previous studies that compare the lipid and glucose levels in outpatients with those of inpatients except reports from Mitchell *et al.*

and Osborn *et al.* (*8,9*). They reported that the incidence of these life-style related diseases and serum levels of triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and fasting plasma glucose (FPG) in Japanese outpatients were higher than those in inpatients (*10-12*). For example, the rate of metabolic syndrome was 34.2% and 13.0% in outpatients and inpatients, respectively. The mean length of hospitalization of Japanese psychiatric patients was about 300 days in 2011 much longer than such patients in Australia, Europe and North America (mean lengths are below 50 days) (*13*). The long duration of hospitalization may affect the metabolic condition of the patients because of controlled meals, exercise and so on in hospitals. The mean hospitalization time of schizophrenia is approximately 80 days in the psychiatric department of Kohnodai hospital. This is an intermediate hospitalization time between traditional Japan, and Europe and North America.

In this present study, we investigated the similarities and differences of lipid and glucose metabolism in the same patients transferred from hospitalization to outpatients at the psychiatric department of Kohnodai hospital to clarify the metabolic changes of outpatients and inpatients in Japan.

Patients and Methods

Study subjects

The diagnosis of psychiatric disorder was established as follows. Trained psychiatrists carried out a diagnostic interview of the patients and reviewed information from the patients' relatives. A diagnosis was made using the ICD-10 classification. Then, several psychiatrists discussed the assessment of the diagnosis and treatments in every patient at the conference opening every week. We picked up schizophrenia (F20), acute and transient psychotic disorders (F23) and schizoaffective disorders (F25) as schizophrenia group (F2 group).

This study was performed from January 2016 to December 2018 at Kohnodai Hospital, National Center for Global Health and Medicine. Study participants were 144 of F2 group inpatients (62 males and 82 females) and 109 outpatients (45 males and 64 females) in the Psychiatry Department at Kohnodai Hospital. 109 outpatients were followed for approximately 2 years from 144 discharged patients. We selected these 109 persons without changes of administered drugs, which were psychotropic, anti-dyslipidemic and hypoglycemic drugs during these 2 years. Then, these outpatients were the same inpatients except for 35 non-selected persons.

The study protocol was approved by the Ethics Committees of Chiba University (No.182) and the National Center for Global Health and Medicine (No.1837). All participants were provided with a written informed consent form, and explanation and participation agreement were performed in accordance with the Declaration of Helsinki principles.

Diagnosis of somatic diseases in study participants

Diabetes mellitus was defined as hemoglobin A1c (HbA1c) over 6.5% and FPG over 126 mg/dL (*14*). High LDL-cholesterolemia (fasting serum LDL-cholesterol (LDL-C) ≥ 140 mg/dL) or low high density lipoprotein (low HDL)-cholesterolemia (fasting serum HDL-cholesterol (HDL-C) < 40 mg/dL) or hypertriglyceridemia (fasting TG ≥150 mg/dL) were described as dyslipidemia (*15*). Patients were also counted as diabetic if they used hypoglycemic drugs (insulins, glucagon-like peptide-1 receptor agonists, biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidines, dipeptidyl peptidase-4 inhibitors and sodium glucose transporter-2 inhibitors). Patients using statin and/or ezetimibe were counted as hyper LDL-cholesterolemia and those using fibrates were hypertriglyceridemia.

Data collections

Information on patients' demographic data was obtained from their medical records. Body mass index (BMI) was calculated by their height and weight. Blood samples were obtained from patients after 12 h starvation.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), total bilirubin (T-Bil), blood urea nitrogen (BUN) and creatinine (Cr) levels were measured using the consensus method of the Japan Society of Clinical Chemistry (JSCC) (*16*). Total cholesterol (TC), TG and FPG were assayed by enzymatic method and high density lipoprotein-cholesterol (HDL-C) was by direct method. LDL-C was calculated by Friedewald formula from TC, TG and HDL-C (TC-TG/5-HDL-C) and non-HDL cholesterol (non-HDL-C) was TC minus HDL-C. HbA1c was measured by the high performance liquid chromatography (HPLC) method. Estimated glomerular filtration rate (eGFR) was calculated by serum creatinine level, age and gender (*17*).

Data from outpatients were obtained at approximately 6 months, 1 year and 2 years after their discharge.

Statistics

Data from inpatients and outpatients were compared by paired *t* test.

Results and Discussion

Profile of study participants

Table 1 shows the profile of study patients. 109 outpatients were followed during 2 years without changes of administered drugs from 144 inpatients. The ratio of

male to female was 1:1.42 (45 persons: 64 persons) and the average age was 51.3 years old in outpatients. The ratio of hypertriglyceridemia was significantly higher in the outpatient group compared to the inpatient group.

Blood parameters of study participants in hospitalization and outpatients 2 years after their discharge

Table 2 shows serum blood levels of lipids and glucose, and liver and renal functions in patients with hospitalization (inpatients) and outpatients approximately 2 years after their discharge. We chose patients, which had blood parameters both during hospitalization and as outpatients 2 years after their discharge. Outpatients showed significantly higher levels of TC, TG and non-HDL-C than inpatients, accompanied with an increase of body weight and BMI. Serum HDL-C and LDL-C levels had no significant difference between inpatients and outpatients. Indicators of glucose metabolism, FPG and HbA1c were not significantly different in both groups.

Table 1. Profile of study participants

Variables	Inpatients	Outpatients
Cases (*n*)	144	109
Male	62	45
Female	82	64
Age, years (means ± SD)	49.3 ± 11.7	51.3 ± 11.7
Male	47.0 ± 11.2	49.0 ± 11.6
Female	50.9 ± 11.9	52.9 ± 11.7
Diagnosis of physical disorders (ratio)		
Diabetes mellitus	0.160	0.138
Dyslipidemia		
High LDL-cholestrolemia	0.264	0.284
Low HDL-cholesterolemia	0.209	0.202
Hypertriglyceridemia	0.210	0.358*

*indicates significant difference ($p < 0.05$) between inpatient and outpatient groups.

There were no significant differences in parameters of liver function, AST, ALT, γ-GTP and T-Bil between inpatients and outpatients. Concerning renal function, BUN, Cr and eGFR had no significant differences between both groups.

Changes of blood parameters of patients transferred from hospitalization to outpatient care 6 months, 1 year and 2 years after their discharge

Table 3 shows serum blood levels of lipid and glucose, and liver and renal functions in patients with hospitalization and outpatients approximately 6 months, 1 year and 2 years after their discharge. We chose patients, which had blood parameters at hospitalization and all these 3 points after their discharge. Outpatients from either point of 6 months, 1 year or 2 years after their discharge showed significantly higher levels of TC and TG compared with inpatients (Table 3-A). Serum non-HDL-C was significantly higher in outpatients from either point of 6 months or 1 year after their discharge than inpatients. However, serum LDL-C and HDL-C in outpatients were not significantly changed at either point compared with those in inpatients. There were also no significant differences of FPG and HbA1c between either point of outpatients and inpatients (Table 3-B).

As for liver function parameters, serum levels of AST, γ-GTP and T-Bil were not significantly different between inpatients and outpatients at 6 months, 1 year and 2 years after their discharge (Table 3-C). Serum ALT was only significantly increased in outpatients 1 year and 2 years after their discharge compared with inpatients. Concerning renal function, serum levels of BUN had no significant difference between inpatients and outpatients (Table 3-D). Serum Cr and eGFR also showed no significant differences between inpatients and outpatients except for 1 year after their discharge. Significant

Table 2. Blood parameters of study participants in hospitalization and outpatients

Variables	*n*	Inpatients	Outpatients	*p* value
TC (mg/dL)	89	190.1 ± 43.4	200.0 ± 44.3	0.0221
TG (mg/dL)	88	124.5 ± 93.6	168.3 ± 139.0	0.0026
HDL-C (mg/dL)	77	52.5 ± 16.8	52.2 ± 15.6	NS
LDL-C (mg/dL)	80	113.8 ± 37.8	115.5 ± 37.1	NS
Non-HDL-C (mg/dL)	77	138.8 ± 44.3	148.7 ± 45.7	0.0336
FPG (mg/dL)	91	113.4 ± 26.9	118.8 ± 31.8	NS
HbA1c (%)	91	5.83 ± 0.72	5.88 ± 0.78	NS
AST (IU/L)	96	33.9 ± 65.0	22.4 ± 12.6	NS
ALT (IU/L)	95	28.0 ± 27.9	26.4 ± 23.3	NS
γ-GTP (IU/L)	64	48.4 ± 67.6	57.4 ± 152.6	NS
T-Bil (mg/ dL)	73	0.610 ± 0.697	0.488 ± 0.230	NS
BUN (mg/ dL)	96	11.6 ± 5.55	11.4 ± 4.77	NS
Cr (mg/ dL)	96	0.691 ± 0.217	0.706 ± 0.237	NS
eGFR (mL/min)	96	87.6 ± 22.7	83.5 ± 19.7	NS
Body weight (kg)	28	68.1 ± 17.7	72.6 ± 16.4	0.0318
BMI (kg/m^2)	28	24.6 ± 5.48	26.3 ± 5.54	0.0292

Values are indicated as means ± SD. NS means no significant difference between inpatients and outpatients. It was approximately 2 years between blood examinations of inpatients and outpatients.

Table 3-A. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ lipids ~

Variables	*n*	Means ± SD (mg/dL)	*p* value
TC-0	42	183.1 ± 35.6	
TC-0.5	42	202.5 ± 39.6	0.0032
TC-1	42	200.6 ± 39.1	0.0028
TC-2	42	199.3 ± 40.9	0.0155
TG-0	39	107.9 ± 89.1	
TG-0.5	39	151.6 ± 95.5	0.0081
TG-1	39	151.6 ± 98.9	0.0200
TG-2	39	155.3 ± 121.2	0.0331
HDL-C-0	33	53.9 ± 17.9	
HDL-C-0.5	33	56.3 ± 14.5	NS
HDL-C-1	33	56.0 ± 16.4	NS
HDL-C-2	33	54.8 ± 16.4	NS
LDL-C-0	32	107.6 ± 35.1	
LDL-C-0.5	32	114.1 ± 32.0	NS
LDL-C-1	32	113.5 ± 32.6	NS
LDL-C-2	32	114.3 ± 31.4	NS
Non-HDL-C-0	32	133.0 ± 40.0	
Non-HDL-C-0.5	32	149.0 ± 41.6	0.0153
Non-HDL-C-1	32	144.9 ± 37.7	0.0483
Non-HDL-C-2	32	143.2 ± 34.2	NS

TC (TG, HDL-C, LDL-C or non-HDL-C)-0, -0.5, -1 and -2 mean serum TC (TG, HDL-C, LDL-C or non-HDL-C) levels at inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-B. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ glucose ~

Variables	*n*	Means ± SD	*p* value
FPG-0	43	109.6 ± 20.3 (mg/dL)	
FPG-0.5	43	115.8 ± 23.8	NS
FPG-1	43	113.9 ± 20.1	NS
FPG-2	43	118.5 ± 26.8	NS
HbA1c-0	40	5.84 ± 0.56 (%)	
HbA1c-0.5	40	5.80 ± 0.44	NS
HbA1c-1	40	5.83 ± 0.48	NS
HbA1c-2	40	5.87 ± 0.61	NS

FPG (or HbA1c)-0, -0.5, -1 and -2 mean serum FPG (or HbA1c) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-C. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ liver function ~

Variables	*n*	Means ± SD	*p* value
AST-0	38	21.3 ± 20.3 (IU/L)	
AST-0.5	38	19.2 ± 11.2	NS
AST-1	38	21.7 ± 9.12	NS
AST-2	38	20.8 ± 9.17	NS
ALT-0	38	20.4 ± 16.0(IU/L)	
ALT-0.5	38	22.4 ± 21.0	NS
ALT-1	38	25.9 ± 17.1	0.0096
ALT-2	38	25.3 ± 17.2	0.0329
γ-GTP-0	29	32.4 ± 39.6 (IU/L)	
γ-GTP-0.5	29	28.4 ± 26.3	NS
γ-GTP-1	29	28.9 ± 31.4	NS
γ-GTP-2	29	30.4 ± 25.3	NS
T-Bil-0	26	0.428 ± 0.277 (mg/dL)	
T-Bil-0.5	26	0.406 ± 0.199	NS
T-Bil-1	26	0.472 ± 0.176	NS
T-Bil-2	26	0.427 ± 0.254	NS

AST (ALT, γ-GTP or T-Bil)-0, -0.5, -1 and -2 mean serum AST (ALT, γ-GTP or T-Bil) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-D. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ renal function ~

Variables	*n*	Means ± SD (mg/dL)	*p* value
BUN-0	48	11.3 ± 4.75	
BUN-0.5	48	11.4 ± 4.25	NS
BUN-1	48	11.3 ± 3.23	NS
BUN-2	48	11.3 ± 3.75	NS
Cr-0	48	0.647 ± 0.172	
Cr-0.5	48	0.667 ± 0.152	NS
Cr-1	48	0.681 ± 0.157	0.0307
Cr-2	48	0.660 ± 0.141	NS
eGFR-0	48	89.3 ± 23.3	
eGFR-0.5	48	84.4 ± 19.9	NS
eGFR-1	48	82.3 ± 19.2	0.0092
eGFR-2	48	84.7 ± 20.0	NS

BUN (Cr or eGFR)-0, -0.5, -1 and -2 mean serum BUN (Cr or eGFR) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

increasing Cr and decreased eGFR were observed in outpatients 1 year after their discharge compared with inpatients.

The present study shows that Japanese schizophrenic patients transferred from hospitalization to outpatient care have increased serum TC, TG and non-HDL cholesterol levels during 2 years after their discharge, but no changes of FPG and HbA1c levels for these 2 years.

In our study, serum TG level was significantly increased in outpatients than in inpatients accompanied with an increase of body weight and BMI in outpatients, similar to other Japanese reports (*10,11,18*). Recent reviews indicated that serum TG levels of schizophrenic inpatients were almost the same as controls, but those of outpatients were increased by 30-40% compared with controls (*19,20*). The differences of TG levels between outpatients and inpatients might be related to the circumstances of hospitalization, because serum TG levels are easily influenced by exogenous factors such as exercise and/or diets.

Cholesterol in the body is mainly derived from internal cholesterol synthesis (*21*). External diet uptake contributes to body cholesterol by only 10-30% (*22*). Furthermore, serum LDL-C level is regulated by VLDL synthesis in the liver and LDL-receptor uptake in various tissues (*23*). It is probable that serum LDL-C is hard to change by exogenous factors compared to serum TG. Serum LDL-C level of outpatients in our study was almost the same as in Sugai's paper (LDL-C: 115.5 mg/dL *vs.* 117.6 mg/dL, respectively) (*11*). But, those levels in inpatients were higher in our study than Sugai's paper (LDL-C: 113.8 mg/dL *vs.* 106.9 mg/dL,

respectively) (*11*). The mean hospitalization time is 80 days in Kohnodai hospital, which is much shorter than their report (mean hospitalization time is over 300 days). This long hospitalization might be related to changes of life-style and severity of psychotic symptoms, which induce weight loss and decreased synthesis of cholesterol (*18*). Therefore, these results suggest that there are some differences of lipid metabolism between inpatients and outpatients in Japan.

Serum TC contains mainly LDL-C, HDL-C and cholesterol of VLDL or remnant lipoproteins. Even though, LDL-C and HDL-C were almost the same levels between inpatients and outpatients, suggesting that VLDL and/or remnant lipoproteins are increasing in outpatients. This is one of the reasons why non-HDL-C level was increased in outpatients because cholesterol of VLDL and remnant lipoproteins are counted as non-HDL-C.

Serum HDL-C levels have complex mechanisms. Usually, serum high TG levels were accompanied with serum low HDL-C levels because TG and cholesterol are exchanged in HDL by cholesterol ester transfer protein (*24*). But, this is not the case. Outpatients showed high serum TG levels but no significant changes of serum HDL-C compared with inpatients. HDL-C metabolism in psychiatric patients still remains to be elucidated.

Concerning glucose metabolism, FPG and HbA1c levels were not significantly changed during the 2 years after their discharge (FPG: from 113.4 mg/dL to 118.8 mg/dL; HbA1c: 5.83% to 5.88%, inpatients to outpatients, respectively), this is different from Sugawara's report (*10*). FPG level of inpatients was 90.6 mg/dL in their report, which is lower than our study, in accordance with the long hospitalization time. That of outpatients in their report was 115.7 mg/dL, similar to our study. As described by Kanzaki *et al.* (*25*), FPG and HbA1c levels were already significantly higher in Kohnodai hospitalized psychiatric patients compared with the Japanese standard. Therefore, we need to follow glucose metabolism in outpatients.

Concerning liver functions, AST, γ-GTP and T-Bil were not significantly changed until 2 years after discharge. ALT was significantly increased at 1 year and 2 years after discharge. These increases are within standard levels (< 30 IU/L). eGFR was significantly decreased and serum creatinine level significantly increased after 1 year from their discharge. This tendency was also observed at 6 months and 2 years after their discharge. High blood pressure is one of the causes of renal dysfunction (*26*). We did not check blood pressure in all outpatients, but systolic and diastolic blood pressure had a tendency to be higher in outpatients than inpatients (data not shown). We need to check and follow liver functions, renal functions and blood pressure as well as lipid and glucose metabolism in outpatients with schizophrenia.

This study also has some limitations. First, it was an observation study. It is impossible to clarify the cause-effect relationship between life-style related conditions and increased serum TC and TG. Second, follow up period in outpatients was 2 years. We need to catch changes of glucose metabolism, renal and liver functions for a long time follow up in outpatients.

In conclusion, we found that serum triglycerides, total cholesterol and non-HDL cholesterol levels of schizophrenic patients were increased, but blood glucose and HbA1c levels were not changed during 2 years after their discharge.

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Underlying causes of underutilization of maternal, neonatal and child health (MNCH) services in Africa: A survey from Lagos State, Nigeria

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Abstract: Lagos State, Nigeria, Africa's largest city with an estimaed 21 million population, continues to face challenges in its attempts to reduce maternal mortality (555 deaths per 100,000 live births) and deaths of children under five (59 per 1,000 live births). These deaths are more common among women and children living in poverty, many of whom rarely utilize health services. This paper describes the trend in the use of maternal, neonatal and child health (MNCH) services in the State in the past decade and shows barriers to the use of the services. Significant improvement in the coverage of the services were not observed. We identified the following five types of barriers to the use of MNCH services: *i*) financial barriers, *ii*) physical barriers, *iii*) cognitive barriers, *iv*) organizational barriers, and *v*) psychological and socio-cultural barriers. To address these interrelated barriers, the Lagos State Ministry of Health should prioritize regular outreach health services including health promotion, and realize the current initiative for massive recruitment of health personnel and appropriate deployment of them.

***Keywords*:** health seeking behaviour, barriers to health services, qualitative study, Nigeria

Introduction

Despite the currently reported global decreases in maternal deaths (*1*) and deaths of children under five (*2*), certain regions of the world are still struggling to reduce their local rates of maternal and early childhood death. Developing countries account for 99% of global maternal deaths (*1*) and under-five deaths (*2*). Sub-Saharan Africa alone accounts for 62% of global maternal deaths (*1*) and 50% of global under-five deaths (*2*). At the country level, India and Nigeria together were estimated to account for one-third of all maternal (*1*) and under-five deaths worldwide in 2013 (*2*).

In Lagos State, Nigeria, Africa's largest city with an estimaed 21 million population, the maternal mortality ratio (MMR) remained high at 555 per 100,000 live births according to the latest data available as of 2020 (*3*). Change in the MMR in the State in the past decade is not known yet. At the national level, the MMR in 2018 was almost the same as in 2008 as the MMR confidence intervals (CIs) overlap for the 2008 and 2018 surveys (*4,5*). The under-five mortality rates (U5MRs) in the State in 2011 and 2018 were 65 (*6*) (no CI available) and 59 (CI: 46-73) (*5*) per 1,000 live births, respectively. Significant improvement in the U5MR in the State was not observed during the period, either. These figures widely range across the Local Gernment Areas (LGAs) within the State (*3*). A recent cross-sectional study conducted in slum areas in the State shows high MMR at 1,050 per 100,000 live births and U5MR at 103 (*7*).

This paper aims *i*) to describe trend in utilization of maternal, neonatal and child health services in Lagos State in the past decade, *ii*) to show barriers to utilization of the services identified in our previous study, and *iii*) to discuss policy implications.

Trend in the utilization of maternal, neonatal and child health services in Lagos State

Table 1 shows trend in the utilization of maternal, newborn and child health (MNCH) services in Lagos State. The proportion of deliveries in health facilities in the State has been relatively high at 79% between 2011 and 2017 (*6,8*). Percentages of women and births with a postnatal check in the first two days after birth decreased and increased between 2013 (*9*) and 2018 (*5*), respectively. Yet, as CIs are not available for the

Table 1. Trend in the utilization of maternal, newborn and child health services in Lagos State

Type of services	2011 (%) (*Ref. 6*)	2013 (%) (*Ref. 9*)	2017 (%) (*Ref. 8*)	2018 (%) (*Ref. 5*)
Delivery in health facility	79.3		79.5	
Poorest			68.1	
Poor			69.7	
Middle			80.2	
Rich			86.7	
Richest			93.1	
Postnatal checkup for mothers		83.9		72.8
Postnatal checkup for newborns		57.9	79.8	66.8
Poorest			65.8	
Poor			71.1	
Middle			80.7	
Rich			90.6	
Richest			89.5	
Immunization		53.9	63.2	62.4
Poorest			49.8	
Poor			57.0	
Middle			58.2	
Rich			80.4	
Richest			83.0	

indicators, it is unclear that the changes are statistically significant. The same applies to immunization coverage although it increased by 8.5% during the same period. It should be noted that there are large inequities in regard to the coverage of MNCH services across wealth quintiles. This is likely one reason why more maternal and under-five deaths in the State occur among women and children living in poor conditions, as has also been observed globally (*10*). The majority of these deaths are preventable through services available at the primary healthcare level. Given that the public primary health centres (PHCs) provide free or relatively inexpensive health services, it would be beneficial for the poor to utilize the MNCH services available at the PHCs.

In view of the current low rates of MNCH access, it is worth identifying barriers to the utilization of the services among the poor. A quantitative study is not typically designed to provide insights into the underlying causes of non-use of services. Qualitative data are helpful to interpret the underlying causes of the limited use of MNCH services in the State.

Barriers to utilization of MNCH services in Lagos State

We conducted a qualitative study in four deliberately selected slum settlements in Lagos State in December 2014. Data was collected through 24 semi-structured interviews (12 males and 12 females) and seven focus group discussions (15 males and 20 females). The qualitative data obtained were coded and categorized. We identified the following five types of barriers to the use of MNCH services: *i*) financial barriers, *ii*) physical barriers, *iii*) cognitive barriers, *iv*) organizational barriers, and *v*) psychological and socio-cultural barriers. To understand the underlying barriers, the authors mapped out them by confirming the linkages between them (Figure 1), which could contribute to the lower use of services.

Financial barriers

Starting from the left of Figure 1, "Unaffordable health service costs" is related to "High opportunity costs" such as travel cost and lost profits due to suspension of business.

Physical barriers

Regarding "Poor accessibility to health facilities", due to the limited number of pedestrian bridges over major roads in the study area, some people choose not to visit a public PHC on the other side of a major road due to the "risky road crossing".

Cognitive barriers

When women and caregivers are not aware of the need for MNCH services (Limited awareness of the need), they may not notice the availability of health facilities and services in their community (Limited knowledge about health facilities/services available).

Organizational barriers

"Limited availability of health facilities/services/staff in the community" is an obvious barrier to the use of MNCH services. Even when services are available at health facilities, however, the issue of "Limited staff" may prevent facilities from attending to their many clients in a friendly and attentive manner (Poorer behaviour of public health professionals) and also leads to "Long waiting times". "Limited staff" at public PHCs also prevents staff from taking the time to

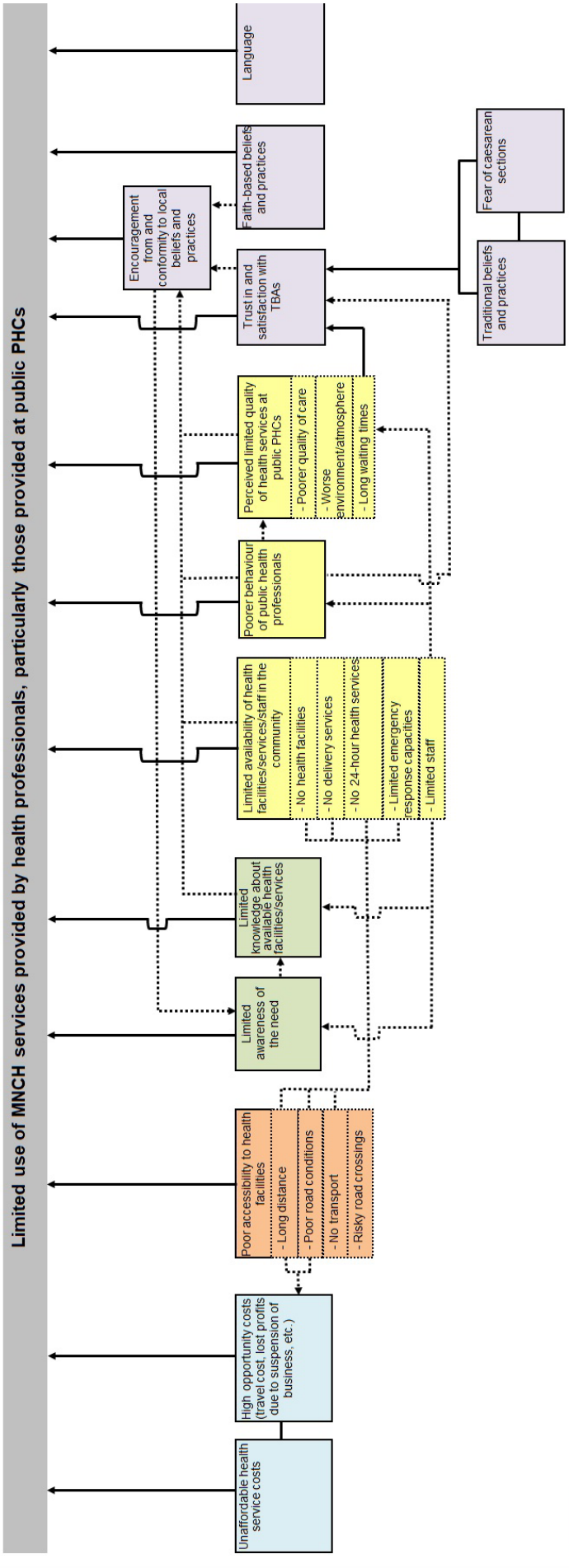

Figure 1. Barrires to use of MNCH services and interactions amongst the barriers

conduct regular outreach health activities. Therefore, the issue of "Limited staff" could be an underlying cause of "Limited awareness of the need" and "Limited knowledge about available health facilities/services". In Lagos State, health professionals are in short supply and unevenly distributed. It is estimated that the majority of doctors and nurses/midwives in public and private health facilities in the State work for higher level health facilities (*i.e*. secondary and tertiary hospitals) (*3*). The scarcity of community health extension workers (CHEWs) is an additional critical issue. CHEWs are crucial in increasing the use of and demand for health services.

"Poorer behaviour of public health professionals" could downgrade the perceived value of public PHCs (Perceived limited quality of health services at public PHCs), which could discourage people from using the PHCs again. Our data also showed that "Long waiting times" contribute to the preference for traditional birth attendants (TBAs) (Trust in and satisfaction with TBAs), which could also be partially attributable to "Poorer behaviour of public health professionals".

Respondents tended to perceive the limited types of medical equipment and numbers of drugs as an indicator of "Poorer quality of care", regardless of whether a public PHC actually needs a wide variety of equipment and drugs to be effective. They also had the impression that a public PHC has a "Worse environment and atmosphere".

Psychological and socio-cultural barriers

"Traditional beliefs and practices" and "Fear of caesarean sections" are interrelated and seem to be the underlying causes of "Trust in and satisfaction with TBAs".

Since traditional practitioners including TBAs are acquainted with herbal medicines and rituals (Traditional beliefs and practices) in accordance with the needs of the local community, they are recognized as individuals who have an important role to play in ensuring desirable health outcomes (*11*).

"Fear of caesarean sections" is a specific barrier to the use of facility delivery services. In Nigerian culture, the inability to achieve vaginal delivery is regarded as the failure of a woman's reproductive functions (*12*).

In Nigeria, faith-based clinics are patronized by many women for maternal health services (Faith-based beliefs and practices) for various reasons such as the desire for spiritual protection against satanic attacks during delivery, lower financial burdens and the harsh attitudes of health professionals (*13*).

"Encouragement from and conformity to local beliefs and practices" could be attributable to "Limited knowledge about available health facilities/services", all types of organizational barriers, "Trust in and satisfaction with TBAs" and "Faith-based beliefs and practices", as these factors likely shape the opinions of community members on health services provided by health professionals and/or public PHCs. Furthermore, "Encouragement from and conformity to local beliefs and practices" is likely to contribute to "Limited awareness of the need", as people who should seek care may not perceive the need if their neighbours are not aware of the need.

For those who immigrate from outside Lagos State and have difficulty in communicating in Yoruba or English, "Language" is one of the barriers to accessing MNCH services.

Policy discussion

Our analyses pointed to several intervention options that we recommend to the State Ministry of Health.

To address the issus of financial, cognitive and physical barriers, regular outreach health services along with health education and promotion could be an option to enable the poor to receive MNCH services, to be enlightened and to minimize their expenditures in seeking care.

Regarding the issue of "Limited availability of health facilities/services/staff in health facilities", in 2013, Lagos State launched an initiative to establish Comprehensive PHCs in all 57 administrative areas that provide 24-hour health services including those for MNCH (*14*). The issue of "limited emergency response capacities" is likely to be alleviated once all the Comprehensive PHCs in the State have been renovated. But, only 14 Comprehensive PHCs have been established by 2018 (*15*). The earlier full-scale State-wide establishment of PHCs is expected. The state government has recently commenced mass recruitment of health personnel (*16*). We hope that the newly recruited health personnel will be deployed mainly to public PHCs in proportion to the population size to redress the current problematic distribution (*17*). The State Ministry of Health also recognizes the issue of "Poorer behaviour of public health professionals" and recently provided health workers with training on etiquette (*18*). To reduce the biased "limited quality of health services at public PHCs", communities need to be informed about the particular kinds of health services that a public PHC is intended to provide. Ward Health Committees (WHCs) (in Lagos State, a Ward Health System has been promoted based on Health Sector Reforms established in 2008, and WHCs have been set up since then) could play leading roles in the education process.

Worldwide, there is disagreement about whether training programmes for TBAs are effective in improving MNCH outcomes (*19*). Given that TBAs are in great demand in Lagos State, establishing cooperative ties between TBAs and the formal health system would be a better choice, than attempts to discourage the public from using TBAs or demands for substantial

improvements in TBAs' midwifery knowledge and skills. Some PHCs in the State have regular meetings with TBAs practising in their catchment areas to share information. Such regular interactions could strengthen the cooperative ties between the health system and TBAs and improve referral rates. In Lagos State, "Traditional practices" such as herbal remedies are likely widely used as seen in other Nigerian states (*20*). Yet, some herbal medications may cause teratogenic effects to the fetus (*21*). Assessments of the safety and efficacy of the herbal remedies are needed. Additionally, efforts should be geared towards ensuring that laws are in place in Lagos State that will guide the practice of traditional medicine. To avoid preventable maternal deaths, medically unsuitable "Traditional beliefs" such as the meaning of non-vaginal delivery should be changed through health education. Faith-based clinics are not often properly staffed or well-equipped although they are well patronized. As in the case of TBAs, enhancing collaboration between the health system and "Faith-based" clinics would be an option to improve referral rates. As "Encouragement from and conformity to local beliefs and practices" could be related to various cognitive and psycological and socio-cultural barriers, an approach to health education and promotion that is inclusive of all community members is necessary for MNCH programmes to be successful. To overcome the "Language" barrier, the Lagos State Ministry of Health provides health information in several languages through radio programmes, leaflets and posters, and this should be continued.

Among the intervention options, *i*) regular outreach health services along with health education and promotion, and *ii*) realization of the current initiative for massive recruitment of health personnel and appropritae deployment of them should be the top priorities. Because "Traditional beliefs and practices" and "Limited staff" seem to be the underlying causes of multiple barriers.

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A new challenge of unfractionated heparin anticoagulation treatment for moderate to severe COVID-19 in Japan

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Abstract: Hypercoagulation and anticoagulation treatment have become new challenges in coronavirus disease 2019 (COVID-19) patients during the COVID-19 pandemic. We herein suggest an algorithm for an anticoagulation treatment with unfractionated heparin in moderate to severe COVID-19 cases in Japan, and report a case of COVID-19 pneumonia with anticoagulation treatment. Although several promising drugs for COVID-19 are being tested in clinical trials, definitive treatments have not yet been established. In this report, we demaonstrate that anticoagulation treatment with unfractionated heparin has the possibility of becoming at least a supportive treatment for COVID-19 patients.

***Keywords*:** COVID-19, hypercoagulation, anticoagulation treatment, unfractionated heparin

Introduction

With coronavirus disease 2019 (COVID-19) being a global threat (*1*), several case reports, including autopsy series, show that patients with COVID-19 experience pulmonary embolism (PE) (*2-4*). Although several promising drugs for COVID-19 are being tested in clinical trials, a definitive treatment has not yet been established (*5*). A previous study with 449 patients indicated that anticoagulation (AC) treatment using low molecular weight heparin (LMWH) and unfractionated heparin (UFH) was associated with decreased mortality in severe COVID-19 patients with coagulopathy (*6*). Although several facilities around the world have developed an AC algorithm for COVID-19 patients (*7-9*), there is no such algorithm nor case reports of COVID-19 patients with AC in Japan. In order to develop such an algorithm, it is necessary to consider which drugs have been approved in a given country. Based on an AC algorithm used in other countries (*7-9*), we herein suggest an AC therapy with UFH for moderate to severe COVID-19 patients in Japan (Figure 1), and report a case of a COVID-19 patient with pneumonia and AC.

Patient and Methods

A healthy 68-year-old male presented to the hospital with a 7-day history of fever, productive cough, and progressing dyspnea. The physical examination revealed a body temperature of 37.1°C, blood pressure of 124/76 mmHg, pulse of 94 beats per minute, respiratory rate of 24 breath per minute, and oxygen saturation of 91% in ambient air. In addition to lymphopenia (7.1%), laboratory testing revealed that the lactate dehydrogenase (440 U/L) and C-reactive protein (11.7 mg/dL) concentrations were elevated, while the d-dimer level was normal (< 0.5 μg/mL). A chest computed tomography (CT) scan showed bilateral multifocal peripheral ground-glass opacities; thus, the patient was diagnosed with COVID-19 by reverse transcription polymerase chain reaction. We administered hydroxychloroquine (200 mg BID), methylprednisolone (1 mg/kg/day), oxygen at 1 liter per minute (LPM), and systemic prophylactic dosing (10,000 IU/day) of UFH. As his oxygen requirement increased to 4 LPM by hospital day (HD) 5, and his d-dimer level increased to 10.9 μg/mL, UFH was initiated for therapeutic dosing (10,000 IU/day with a target of 1.5 to 2.5 times the activated partial thromboplastin time [aPTT]). After the patient was started on UFH, his oxygen requirement and d-dimer level gradually decreased. As oxygen administration was halted when his d-dimer level decreased to 2.0 μg/mL and he could move by himself on HD 11, UFH was terminated without any adverse events (the duration of UFH for therapeutic dosing was 7 days).

Discussion

We herein suggest an AC treatment using UFH in moderate to severe COVID-19 cases in Japan (Figure

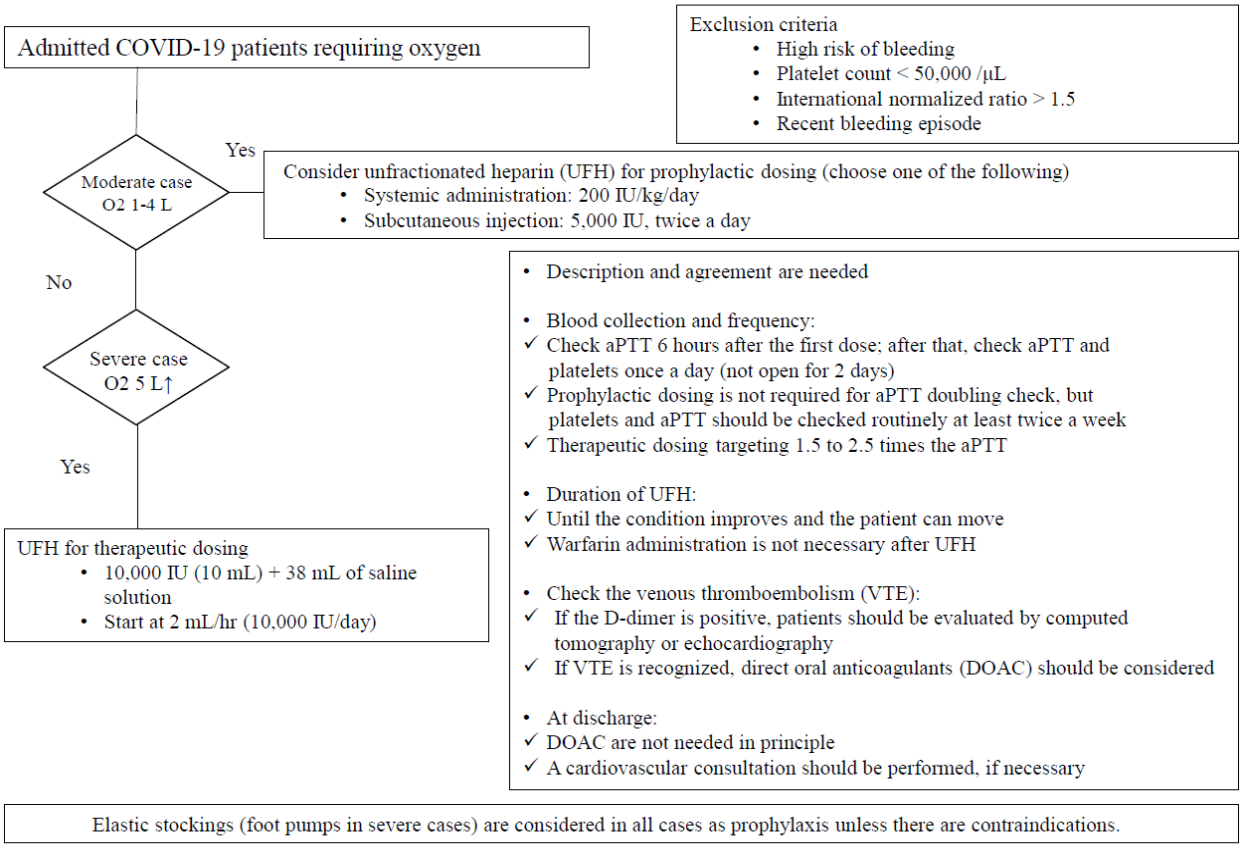

Figure 1. Algorithm for unfractionated heparin anticoagulation treatment in patients with moderate to severe COVID-19. This figure shows the algorithm for unfractionated heparin anticoagulation therapy in patients with moderate to severe COVID-19 that can be used safely in Japan.

1), while showing that intubation was avoided in a high-risk patient using AC. Although the pathogenesis of COVID-19 has not yet been elucidated, the clinical stage of the disease is thought to be divided into three phases: the viremia phase, the acute phase, and the recovery phase (*10*). AC may be especially recommended for patients in the viremia and acute phases (*10*) as the disease itself and inflammation as well as other factors may lead to excessive activation of coagulation in these phases (*6,11*).

In a study supporting AC therapy as an effective treatment for COVID-19, veno-venous extracorporeal membrane oxygenation (VV-ECMO) is reported as one of the treatments of severe COVID-19 which is thought to be possibility of comorbid PE has been pointed out (*12*). VV-ECMO may have been useful in AC. The one of the reasons for it are that the therapeutic effect of VV-ECMO is not direct treatment of respiratory failure, but UFH which is used to maintain the circuitry of VV-ECMO may treat for PE of severe COVID-19 (*12*). Previous autopsy case series have also reported embolism in the lung of a COVID-19 patient (*4*).

Although we suggest AC therapy with UFH as treatment for moderate to severe COVID-19 cases, several issues with AC therapy remain and should be addressed in the future. First, the practical application aof AC with UFH, including indications, dosage, and duration of AC, should be explored further. Although one algorithm recommends AC for all patients with COVID-19 (*8*), we suggest considering prophylactic dosing of UFH (systemic administration of 200 IU/kg/day or subcutaneous injection at 5,000 IU, twice a day) for moderate COVID-19 patients requiring 1-4 liters of oxygen and therapeutic dosing (systemic administration of 200 IU/kg/day with a target of 1.5 to 2.5 times the aPTT) for severe COVID-19 patients requiring more than 5 liters of oxygen. The recommended duration of UFH is until the patient's condition improves and the patient can move. As AC treatment is currently controversial, clinicians should consider the risk of bleeding as well as post-discharge treatment. The Mount Sinai algorithm calls for treatment with direct oral anticoagulants (DOAC) for 2 weeks after the patient has been discharged (*9*). However, there is no indication for DOAC use for COVID-19 in Japan. Additionally, as DOAC is a new drug, interactions with COVID-19 therapies as well as the high costs must be considered. Despite these issues, we suggest an UFH AC treatment algorithm for moderate to severe COVID-19 cases that can be used safely in Japan (Figure 1).

Our study has several limitations. First, we report only one case of COVID-19 with AC. Second, adequate

assessment of thrombosis using an enhanced CT scan and an ultrasound scan before treatment with AC was not carried out due to restrictions associated with infection prevention and control. Third, the therapeutic impact of AC on COVID-19 pneumonia cannot be confirmed by this report alone as there were many confounding factors, such as patient demographics and anti-COVID-19 therapies. However, given the hypercoagulability of COVID-19 patients and the clinical impact of AC observed in previous studies (*6,10*), at a minimum, AC may be used as supportive therapy for COVID-19 patients.

In conclusion, this is the first report of an AC treatment algorithm for patients with moderate to severe COVID-19, and the first successfully recovered case of COVID-19 with AC in Japan. Hypercoagulation and AC in COVID-19 patients is thought to be a new challenge (*13*). With the current large numbers of COVID-19 cases, further studies that explore the improvement of AC algorithms and evaluation of the therapeutic impact of AC using multivariate analysis are expected.

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Corticosteroid therapy for severe COVID-19 pneumonia: optimal dose and duration of administration

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Abstract: Severe COVID-19 is associated with a hyperinflammatory state, and corticosteroid therapy may be effective. We review the recent literature and discuss the appropriate dose and duration of corticosteroid therapy. Low-dose corticosteroid therapy is often used to treat COVID-19. However, several doses of methylprednisolone (or prednisolone) have been attempted, ranging from about 40 mg/day to 2 mg/kg/day. Doses may need to be adjusted depending on severity. Corticosteroid therapy is generally administered for a short period over several days. However, COVID-19-induced respiratory failure is often prolonged, so longer administration may be considered. Careful monitoring for complications due to corticosteroid therapy is vital.

***Keywords*:** COVID-19, SARS-CoV-2, corticosteroid therapy, acute respiratory distress syndrome, viral RNA clearance, complications

Introduction

The outcome for patients with COVID-19 who require mechanical ventilation is extremely poor. For example, 88% of such patients in New York City are reported to have died (*1*). Antiviral drugs and vaccines are awaited, but until those become available, the establishment of organ support therapies is also desirable. Considering that a hyperinflammatory state may be involved in severe COVID-19 (*2*), anti-inflammatory therapy may be effective.

The use of systemic corticosteroid therapy for COVID-19 is controversial. In Middle East respiratory syndrome, which like COVID-19 is caused by a coronavirus, corticosteroid therapy has been reported to be associated with decreased viral RNA clearance in respiratory secretions (*3*). Therefore, many clinicians are cautious about corticosteroid administration, even in patients with COVID-19. However, in a single-center observational study in Wuhan, the use of methylprednisolone was associated with decreased mortality (*4*). In a non-peer reviewed observational study (*5*), Wang *et al*. reported that the use of methylprednisolone was associated with early recovery of oxygen saturation. Citing that report, the Surviving Sepsis Campaign Guidelines suggested that corticosteroid therapy might be effective in patients with COVID-19 who require mechanical ventilation (*6*).

The optimal steroid therapy protocol for COVID-19 is not yet known, so here we review the recent literature and discuss the effectiveness, appropriate dosing, and duration of corticosteroid therapy for COVID-19 pneumonia.

Dose

Steroid therapy may reduce the mortality rate of severe pneumonia (*7,8*), with corticosteroids mainly administered as prednisolone 40-50 mg/day or hydrocortisone 240 mg/day. However, COVID-19 pneumonia with organ failure almost always meets the diagnostic criteria for acute respiratory distress syndrome (ARDS). The conventional corticosteroid dose for ARDS is methylprednisolone 1-2 mg/kg/day (*9,10*). In addition, dexamethasone 20 mg (corresponding to about 80 mg methylprednisolone) has recently been reported to reduce mortality in ARDS (*11*). Moreover, high-dose methylprednisolone (1-2 mg/kg) may be an option.

In a recently reported multicenter observational study, mortality was higher in patients with COVID-19 who received corticosteroids at ≥ 1 mg/kg/day in terms of prednisolone than in those who received no or low-dose corticosteroids (*12*). However, in an additional analysis, steroid dose was not associated with mortality during the first 15 days in critically ill patients only (*13*). This suggests that it may be ideal to adjust the initial dose according to severity. High-dose steroid therapy, at least for mild cases, is not supported.

A number of randomized controlled trials of corticosteroid therapy have been planned (Table 1). A

Table 1. Summary of randomized controlled trials of corticosteroid therapy for COVID-19

NCT number	Country	No.	Intervention	Control
Methylprednisolone < 1 mg/kg/day or equivalent				
NCT04244591	China	80	Methylprednisolone 40 mg, 5 days	Usual care
NCT04263402	China	100	Methylprednisolone < 40 mg, 7 days	Methylprednisolone 40-80 mg, 7 days
NCT04348305	Denmark	1,000	Hydrocortisone, 7 days	Placebo
Methylprednisolone ≥ 1 mg/kg/day or equivalent				
NCT04273321	China	400	Methylprednisolone 1 mg/kg, 7 days	Usual care
NCT04343729	Brazil	420	Methylprednisolone 1 mg/kg, 5 days	Placebo
NCT04325061	Spain	200	Dexamethasone 20 mg, days 1-5 and 10 mg, days 6-10	Usual care
NCT04327401	Brazil	290	Dexamethasone 20 mg, days 1-5 and 10 mg, days 6-10	Usual care

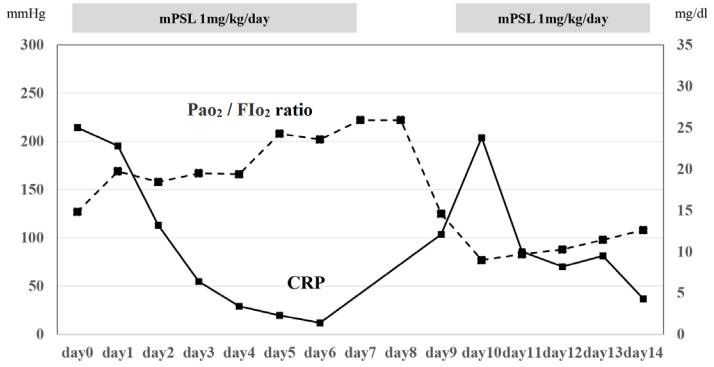

Figure 1. Clincial course of a COVID-19 patient requiring mechanical ventilation and corticosteroid therapy. The patient was admitted and intubated on day 0. She was given methylprednisolone 1 mg/kg/day until day 7. When corticosteroid therapy was stopped, respiratory status and inflammatory response worsened. CRP, C-reactive protein; FIo_2, fraction of inspiratory oxygen; mPSL, methylprednisolone; Pao_2, arterial partial pressure of oxygen.

randomized trial comparing different methylprednisolone doses (< 40 *vs*. 40-80 mg/day) is currently underway (NCT04263402). The results of these trials may soon determine the optimal dose of corticosteroids for COVID-19.

Discussion

Due to concerns about decreased viral RNA clearance, China and the European Society of Intensive Care Medicine (ESICM) have proposed a short treatment duration of 3-5 days. However, in a small retrospective study, short-term administration of corticosteroids was not associated with viral RNA clearance (*14*). It remains unclear whether corticosteroid use is associated with increased SARS-CoV-2 RNA.

COVID-19 pneumonia has a longer clinical course than non COVID-19 pneumonia (*2*). This suggests that a hyperinflammatory state may persist, even as the viral load begins to decline. China's National Health Commission suggests a short treatment period of 3-5 days when using corticosteroid therapy for COVID-19 (*15*). In real-world settings, however, various methods of administration have been attempted. For example, in a phase-3 trial of remdesivir in China, about two-thirds of participants received corticosteroid therapy for a median of 9 days (*16*). This indicates that in some patients with COVID-19, there is some difficulty in withdrawing corticosteroid therapy in a short treatment period.

In addition, an ESICM webinar also noted a biphasic course, with deterioration typically occurring after 5 to 7 days of improvement following the hyperacute phase (*17*). This suggests that longer dosing of corticosteroids may be more beneficial.

We present one of our patients with a characteristic clinical course (Figure 1). She was hospitalized with COVID-19 and immediately intubated for respiratory failure. Treatment was initiated with hydroxychloroquine, broad-spectrum antibiotics, and methylprednisolone 1 mg/kg/day. To improve oxygenation, we terminated methylprednisolone on day 7. However, soon thereafter, hypoxia was exacerbated and inflammatory markers increased, so we restarted methylprednisolone 1 mg/kg/day. Bacterial examination revealed no secondary infection. The long and complicated clinical course of COVID-19 pneumonia has consistently made it difficult to determine whether this should be attributed to corticosteroid discontinuation or the natural course. Such concerns may also arise with short-term administration. We considered that this patient would benefit from

the long-term corticosteroid therapy protocol used for conventional ARDS (10-14 days).

Complications

In addition to the discussion above, complications associated with long-term corticosteroid use cannot be ignored. First, corticosteroid use can cause hyperglycemia. Severe COVID-19 infection has been shown to be more common in diabetics (*1,2*), and corticosteroid use may make glycemic control difficult. Second, long-term corticosteroid therapy may delay improvement in pneumothorax. Gattinoni *et al*. demonstrated two different types of COVID-19 pneumonia according to lung elastance: low elastance or phenotype L and high elastance or phenotype H (*18*). Phenotype H requires high positive end-expiratory pressure and high driving pressure, which increases the risk of barotrauma. In our experience with COVID-19 intubation, pneumothorax or pneumomediastinum occurred in 4/6 (67%) of patients with phenotype H and 2/11 (18%) of patients with phenotype L. In the patients with pneumothorax or pneumomediastinum, long-term corticosteroid therapy may therefore not be appropriate. Third, gastrointestinal bleeding may also be a problem. Moreover, COVID-19 patients may be receiving heparin because venous thromboembolism is a known complication (*19,20*). In addition, it has recently been reported that heparin use is associated with better survival in COVID-19 patients with elevated D-dimer (*21*). Although data are limited, many clinicians are likely to consider anticoagulant therapy in these cases. Other patients may be given high doses of heparin for extracorporeal membrane oxygenation management. The combination of corticosteroids and heparin may increase the risk of gastrointestinal bleeding. Bleeding events have been reported in 7.5% of intubated patients with COVID-19 (*22*).

In summary, the corticosteroid dose is preferably low and adjusted for severity (methylprednisolone 1-2 mg/kg/day). Although short-term treatment is currently the mainstay, we believe that the long-term clinical course of COVID-19 pneumonia suggests that the option of a somewhat longer duration (10-14 days) should be considered.

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LETTER

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COVID-19: emerging challenges for oncological surgery

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Abstract: After the initial description of COVID-19 in Wuhan, China, Italy was hit first in Europe and the impact has been rapidly enlarging. In early April 2020, at the epidemic peak, there were more than 33,000 patients hospitalized including more than 4,000 in Intensive Care Units (ICU). On May 15, the confirmed cases in Italy approached 224,000 patients (5th highest number worldwide), with more than 31,000 deaths (3rd highest number worldwide). Non-urgent, non-cancer procedures were stopped to reallocate nurses and anesthetists to face the COVID-19 emergency. The timeline of the progressive involvement by COVID-19 patients of 36 hospitals referrals for surgical oncology in Italy was shown in this article. Only emergency, and elective oncological procedures were allowed with obvious limitations in terms of numbers of operable cases. Criteria for prioritizing oncologic patients waiting for surgery were released by each region, mainly issuing main factors for decision making, biological aggressiveness or symptomatic disease, the interval from the latest treatment, and the risk of un-resectability if delayed. However, the lack of facilities mostly influenced the decision or not to proceed. The risk of operating on oncological patients with ongoing SARS-CoV-2 syndrome is real, and a preoperative flowchart for ruling out this occurrence has been promoted. In our center, the day before surgery, chest CT and swab testing have been introduced, and a similar behavior has been recommended prior to patients' discharge. The care of patients addressed for surgical oncology should be featured by dedicated paths to secure proper and prompt disease management.

***Keywords*:** COVID-19, SARS-CoV-2, Italy, oncology, surgery, hospital

COVID-19 has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (*1*). Global confirmed cases approached 4,445,000 patients with 302,493 deaths across over 187 countries as of May 15, 2020 (*2*).

After the initial description in Wuhan, China (*3,4*), Italy was hit first in Europe and the impact has been rapidly enlarging with Lombardy and Veneto being the two most affected regions. Italian government ordered a nationwide lockdown effective from March 12, 2020. In early April, at the epidemic peak, there were more than 33,000 patients hospitalized including more than 4,000 in Intensive Care Units (ICU). On May 15, the confirmed cases in Italy approached 224,000 patients (5th highest number worldwide), with more than 31,000 deaths (3rd highest number worldwide) (*2*). Lombardy, the most affected district, suffered from a huge number of severely diseased people overwhelming its capability to absorb the need for care. That, despite Lombardy is one of the most efficient regions within the Italian NHS, recently ranked as the 9th among 195 healthcare systems worldwide (*5*). In this context, a high number of contagions among the hospital health care professionals (HcP) has been reported, with over 10,000 healthcare professional infected and more than 100 physicians died of the disease (*6*). On March 9, the Lombardy lockdown was established, and on March 12 the entire country underwent lockdown, almost completely released on May 18.

Non-urgent, non-cancer procedures were stopped to reallocate nurses and anesthesiologists to face the COVID-19 emergency. This measure freed ventilators for patients with COVID-19 and converted surgical theatres into additional intensive care unit (ICU) beds as needed.

Most surgical departments were closed and converted to medical wards specifically dedicated to COVID-19 patients. More and more surgeons were also requested to help medical personnel in the COVID-19 elective and emergency wards, an absolutely unpredictable event. Figure 1 shows the timeline of the progressive involvement by COVID-19 patients of 36 hospitals referrals for surgical oncology in Italy (*7*).

In this setting, only emergency, and elective oncological procedures were allowed with obvious limitations in terms of numbers of operable cases. Exceeding half of the surgical departments largely decreased their own activity, doubling in most cases the

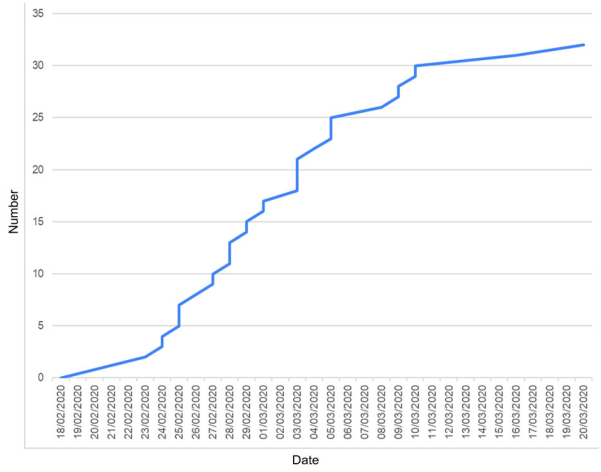

Figure 1. Curve of involvement by COVID-19 infected patients of 36 hospitals referrals for surgical oncology in Italy.

waiting lists (*7*).

Criteria for prioritizing oncologic patients waiting for surgery were released by each region, mainly issuing main factors for decision making, biological aggressiveness or symptomatic disease, the interval from the latest treatment, and the risk of un-resectability if delayed. However, the lack of facilities mostly influenced the decision or not to proceed. The constrain of ICU beds, the lack of expert anesthesiologists emphasized by the need of interventions just for patients with advanced diseases, the reductions of other facilities, as endoscopy, interventional radiology, and radiotherapy hampered the clinically and biologically based prioritization. NHS authorities activated oncological hub-and-spoke programs identifying as Hubs, those hospitals recognized as referrals in surgical oncology, and preferentially not heavily involved in caring for SARS-CoV-2 positive patients. Provided criteria for prioritizing the patients essentially based on tumor biology, tumor burden, therapeutic alternatives, and American Society of Anaesthesiologists (ASA) score risk (*8*), the Hubs should have served for caring for those patients who could not be operated on in those hospitals mostly impacted by the COVID-19 (spoke). Theoretically, wisdom, it partially failed for those Hub centers which resulted also as COVID-19 hospitals, then suffering similar conditions to those affected institutions in need of sharing their oncological waiting lists (*7*). Conversely, the centers, which were able to address the request to be Oncological Hubs were the Cancer Centers without emergency departments. For sure, Cancer Centers physically separated from emergency and infectious disease departments, should be implemented to preserve surgical oncology activity even in conditions similar to that.

The risk of operating on oncological patients with ongoing COVID-19 syndrome is real, a preoperative flowchart for ruling out this occurrence have been promoted. In our center, the day before surgery, chest CT and swab testing have been introduced, and a similar behavior has been recommended prior to patients' discharge.

The risk of healthcare professionals represents something to be considered too. The WHO recommends minimizing the need for personal protective equipment (PPE), and in doing that demands to rationalize its distribution (*9*). However, providing PPE to the healthcare professionals is a priority since in-hospital transmission could deeply undermine their ability to address the request of a system already under significant strain. One third of the departments of surgical oncology in Italy suffered surgeons becoming SARS-CoV-2 positive (*7*), which significantly impacted the working power of the teams. Providing extensive testing for healthcare professionals, and warranting adequate availability of PPE, is also crucial for protecting those patients affected from other problems, and particularly those oncologic. This issue still remains to be addressed in many institutions. Particular attention should be also paid to the safety assessment in the operating room as emphasized by many scientific societies (*10,11*).

Hospital layouts enabling respect for social distance, with paths for patients with infectious disease, and those for oncological patients clearly separated, should be the next target. Existing modalities of telemedicine would help and should probably be implemented to overcome for now and for the future the problem of travelling for many patients. Similarly, it should be done for multidisciplinary meetings, particularly involving multiple centers.

In conclusion, the adaptation of the system did not work adequately. As partial justification, it is worthwhile to be mentioned that the COVID-19 outbreak was really overwhelming. Indeed, Italy has been the country where the COVID-19 outbreak started in the Western world. At that time, it was still an epidemic, and the country did not have benefit of the time needed to better organize an efficient reaction. An option, which was conversely suitable for the other nations despite most of them anyhow heavily suffered the epidemic, which meanwhile became a pandemic (*12*). Preemptive measures such as the acquisition of PPE, and swab test kits, and support to the general practitioners, should have been implemented once the risk of diffusion was advisable. Strengthening the healthcare system within the territory would have been probably helpful in better monitoring the contagion searching for the asymptomatic carrier (*13*), and trying to prevent complications by improved patients' care. Missing all of that we have had to sustain an overwhelming strain for the hospital's network, otherwise well established and internationally recognized: its reaction anyhow allowed to overcome the pandemic peak. This dramatic experience should convey helpful insights for the future. Particularly now, since the outbreak is decrementing, testing the population, treating the patients, and tracking the contagion paths are crucial

rules to erase the risk of a recurrence. In this sense, hospitals, as potential clusters, should be an example of a perfect application of these recommendations. In that, the care of patients addressed for surgical oncology should be featured by dedicated paths to secure proper and prompt disease management.

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Original Articles	~5,000	~10	~50
Brief Reports	~3,000	~5	~30
Reviews	~8,000	~10	~100
Mini reviews	~4,000	~5	~50
Policy Forum articles	~3,000	~5	~30
Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
News	~800	~1	~5

Abstract: ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum); ~150 words (Communications, Editorials, Letters, and News).
Keywords: 3~6 words

Original Articles should be well-documented, novel, and significant to the field as a whole. They should include an abstract and be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

Reviews should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of 100 references and up to 10 figures and/or tables. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references), have no more than 50 references, and have up to 5 figures and/or tables.

Policy Forum articles discuss research and policy issues in areas related to global health and medicine, such as public health, medical care, and social science that may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references), have no more than 30 references, and have up to 5 figures and/or tables.

Communications are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Perspectives", "Comments", or "Correspondence". Communications should not exceed 2,000 words in length (excluding references), have no more than 20 references, and have up to 2 figures and/or tables.

Editorials are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

Letters are articles that provide readers with an opportunity to respond to an article published in *Global Health & Medicine* within the previous two months or to raise issues of general interest to our readers. Letters should provide new information or insights. If appropriate, letters are sent to the authors of the article in question for a response. Letters should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

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The submission to *Global Health & Medicine* should include:

1. Cover letter
2. Main manuscript
3. Figures
4. Supplementary Data, if appropriate

The main manuscripts should be assembled in the following order:

1. Title page
2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
8. List of Supplementary Data, if appropriate

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Please provide all figures as separate files in an acceptable format (TIFF or JPEG). Supplementary Data should also be submitted as a single separate file in Microsoft Word format.

An abstract is necessary for all types of articles. An Original Article should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined. For manuscripts that are Reviews, Policy Forum articles, Communications, Editorials, Letters, or News, subheadings should be used for increased clarity.

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Abstract: The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, Letters, and News, a one-paragraph brief summary of the main content in 150 words or less should be included in the manuscript. Abbreviations must be kept to a minimum and non-standard abbreviations should be explained in brackets at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included on the Abstract page.

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Materials and Methods: The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with Declaration of Helsinki principles. All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

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Discussion: The data should be interpreted concisely without repeating material already presented in the Results section. Speculation is permissible, but it must be well-founded, and discussion of the wider implications of the findings is encouraged. Conclusions derived from the study should be included in this section.

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References: References should be numbered in the order in which they appear in the text. Two references are cited separated by a comma, with no space, for example (*1,2*). Three or more consecutive references are given as a range with an en rule, for example (*1-3*). Citing of unpublished results, personal communications, conference abstracts, and theses in the reference list is not recommended but these sources may be mentioned in the text. In the reference list, cite the names of all authors when there are fifteen or fewer authors; if there are sixteen or more authors, list the first three followed by *et al*. Names of journals should be abbreviated in the style used in PubMed. Authors are responsible for the accuracy of the references. The EndNote Style of *Global Health & Medicine* could be downloaded at Download Center.

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World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_en.pdf* (accessed March 20, 2019).

Tables: All tables should be prepared in Microsoft Word and should be arranged at the end of the manuscript after the References section. Please note that tables should not be in image format. All tables should have a concise title and should be numbered consecutively with Arabic numerals. Every vertical column should have a heading, consisting of a title with the unit of measure in parentheses. If necessary, additional information should be given below the table.

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The manuscript must be accompanied by a cover letter prepared by the corresponding author on behalf of all authors. The letter should indicate the basic findings of the work and their significance. The letter should also include a statement affirming that all authors concur with the submission and that the material submitted for publication has not been published previously or is not under consideration for publication elsewhere. For example of Cover Letter, please visit: Download Centre (*http://www.globalhealthmedicine.com/site/download.html*).

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