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Graphic symbol of ten items in ventilator-associated pneumonia bundle (page 39)

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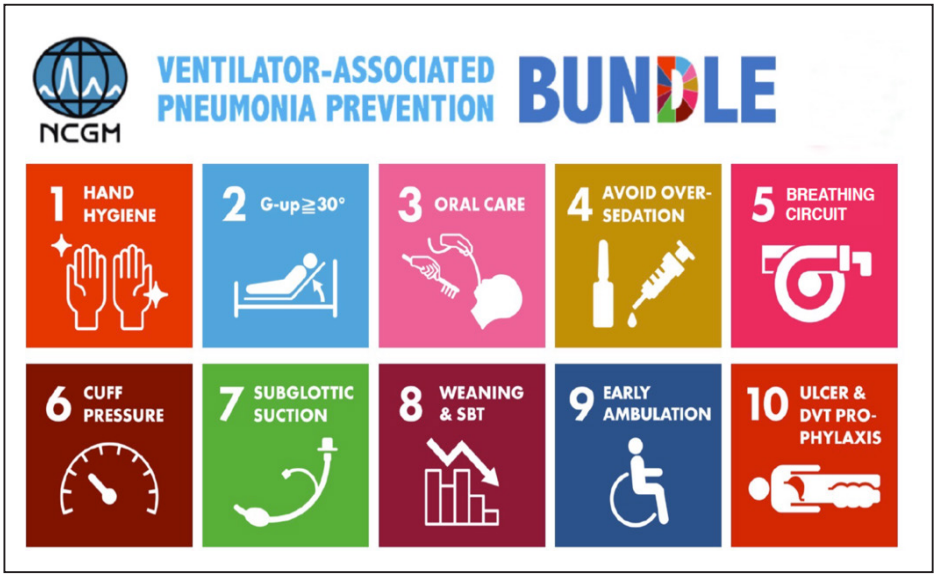

Graphic symbol of ten items in ventilator-associated pneumonia bundle: *i)* hand hygiene, *ii)* head-of-bed elevation (30-45º), *iii)* oral care with cetylpyridinium chloride (CPC), *iv)* avoidance of oversedation, *v)* proper breathing circuit management, *vi)* appropriate maintenance of endotracheal tube cuff pressure, *vii)* closed system and subglottic suctioning, *viii)* daily assessment for extubation, *ix)* early ambulation and rehabilitation, and *x)* peptic ulcer and deep vein thrombosis (DVT) prophylaxis (page 39).

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Advancing the partnership between Japan and Thailand on global health and UHC: "new normal" approach during COVID-19 pandemic

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Abstract: Partnerships, particularly, South-South and Triangular Cooperation play an important role in the 2030 Agenda for Sustainable Development. The Partnership Project for Global Health and Universal Health Coverage (UHC) between Japan and Thailand (the Project) was launched in 2016 as a four-year flagship project for Triangular Cooperation and continued to the second phase in 2020. Participating countries include Asian and African countries who are striving to drive global health and to move towards UHC. However, the COVID-19 pandemic has made coordination of partnerships more difficult. The Project needed to find a "new normal" approach to conduct our collaborative work. Struggling with public health and social measures for COVID-19 has made us more resilient and has increased opportunities to collaborate more closely. In the past year and a half, during the COVID-19 pandemic, the Project successfully conducted a number of online activities between Thailand and Japan and with other countries on global health and UHC. Our "new normal" approach led continuing dialogue of networking both at the project implementation and policy levels, focusing on desk-based activities regarding the targets and the objectives of the project and creating a golden opportunity for pursuing a timely second phase. Our lessons learned include as follows: *i*) Closer prior consultation is required to hold satisfactory online meetings; *ii*) Effective "new normal" approaches include emphasizing practical and interactive discussions on each country's priority issues and expanding target participants; *iii*) Commitment, trust, teamwork, and sharing common goals can enhance and sustain partnerships, especially amid the pandemic.

***Keywords*:** triangular cooperation, new normal, networking

Introduction

Creating partnerships is a cross-cutting goal that can accelerate the implementation of the Sustainable Development Goals (SDGs) (*1,2*). Particularly, the importance of South-South and Triangular Cooperation has been growing as a key modality to strengthen ownership by Southern countries and enhance their capacity to tackle national and global challenges more strategically in sustainable horizontal partnerships (*3,4*).

The world is witnessing globalization of health issues. A wide range of health agendas, including COVID-19, stretches across borders and requires global partnerships, commitments and solutions. Universal Health Coverage (UHC) is a concept whereby all people have access to the health services they need without incurring financial hardship (*5*). Achieving UHC for all by 2030 is one of the key targets of the SDGs. It can enhance a global momentum for health system strengthening as a comprehensive and coherent approach (*6*).

The Partnership Project for Global Health and Universal Health Coverage (The Project) between Thailand and Japan is a good example of Triangular Cooperation in health system strengthening. The expectation of the Project has grown during the COVID-19 pandemic as the world has become more aware that UHC is essential for improving health emergency responsiveness and preparedness. On the other hand, negative impacts of COVID-19, such as travel restrictions and public health agencies being swamped with COVID-19 responses, have limited project activities. Nevertheless, the Project has been moving forward with Thai and international partners. This paper aims to share our "new normal" approach to maintain our work and network during the crisis.

Outline of the Project

Thailand's Ministry of Public Health (MOPH) and

National Health Security Office (NHSO) and the Japan International Cooperation Agency (JICA) launched the Project in 2016 as a four-year flagship project for Triangular Cooperation. Thailand achieved UHC in 2002 ahead of other low- and middle-income countries after Japan did so in 1961. The Project aims to improve UHC operation of Thailand and Japan (Output 1); support other developing countries to achieve UHC (Output 2); and promote strong implementation of UHC globally (Output 3).

In the first phase, areas of collaboration included health finance, health workforce, health information, maternal and child health, and global health. Knowledge sharing through a number of activities led to many successes: for example, a model for developing and managing fee schedules was piloted in Bangkok, which has currently been applied nationwide (Output 1); the first of international training courses on UHC was held, which contributed to networking with 9 participating countries in Asia, the Middle East, and Africa (Output 2); and experience sharing through various international platforms including the Prince Mahidol Award Conference, PMAC, in Thailand, which attracts more than 1,000 health concerned parties from all around the world annually (Output 3) (*7*).

Both Thailand and Japan reaffirmed the critical importance of the collaboration of the two countries and expanding networks. They both agreed to continue to the three-year Phase 2 Project. The outline of the Phase 2 Project was drafted at a working-level meeting in March 2020, around when WHO declared COVID-19 a pandemic, amid growing need for a strong health system to cope with health emergencies. After a thorough process of reviewing the first phase and impact-oriented planning of the second phase, to implement activities more effectively within the limited time under the pandemic and the Project decided to place more focus on health finance and health workforce and to target countries.

"New normal" approach

Almost all of the Project activities were held online because of domestic and international travel restrictions due to COVID-19. In addition to a secure telework environment and digital literature, the following key factors (Figure 1) contributed to successful outcomes.

Focusing on each country's needs

To maximize learning within the limited time available (avoiding the so-called "virtual meeting fatigue" (*8,9*)), we focused on the priority issues and had more practical and interactive discussions rather than teaching theory which can be learned from textbooks. In a workshop with the Ministry of Health (MOH), Lao PDR on their health finance reform, we took a problem-oriented approach, in which a Thai expert gave his ideas about possible solutions based on the situation of Lao PDR, avoiding giving a lecture on how Thailand implemented UHC. Although each session was short, frequent online meetings and proper follow-up could enhance the effectiveness of learning as a whole.

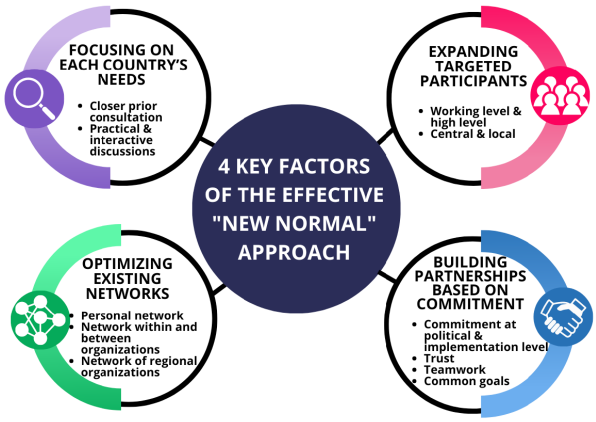

Figure 1. The 4 key factors of the effective "new normal" approach during the COVID-19 pandemic.

The Project served as matchmaker to connect demand and supply sides. Closer prior discussion is critical to identify priority issues from the demand side. Later, the Project can find suitable experts who can impart their knowledge and skill in order to satisfy the practical needs of the collaborating countries.

Expanding targeted participants

The biggest advantage of a virtual meeting is the increased accessibility (no geographical or financial barriers) and unlimited capacity. In the above workshop with the Lao MOH, we could invite officials not only from the headquarters, but also from provincial and local offices. From Thailand, there were also many attendants who could learn from interactive dialogue among the two countries and development partners. The direct involvement of a wide range of concerned people deepened practical discussion and enhanced the effect of mutual learning. In addition, virtual meetings can also facilitate participation of higher-level officials, who are often too busy to travel. Involvement of decision-makers can catalyze actions and facilitate political commitment.

Optimizing existing networks

A difficult part of networking is the initial contact with the counterparts. Building relationships from scratch is hard without in-person communication. The maximum use of the network of Project members and organizations is critical. To realize the above workshop with Lao PDR, a good relationship between the

Project with a JICA expert in Lao PDR and a Project Manager of NHSO with the Lao MOH was beneficial. A workshop on Continuing Professional Development of nurses, where 60 participants and 50 observers from 13 countries were recruited, was successful due to the network of JICA and our partner, Asia-Pacific Action Alliance on Human Resources for Health (AAAH).

The networks and social credit built through the long career of the Project members in health administration, UHC research, bi- or multilateral health cooperation and/or global health diplomacy are our great assets.

Building partnerships based on commitment

The importance of strong policy commitment on the Project grows when the health emergency tends to lower the priority of other issues. Both Thailand and Japan have a strong policy commitment to UHC and global health, and thus to the Project. Thailand set the national Global Health Action Plan (2021-2027) (*10*) to promote the synergy and coherence of Thailand's global health effort and strengthen national health security. Japan also has worked to mainstream UHC in the world through global collaboration and bilateral assistance (*6*). The commitment is visible in the Joint Coordination Committee (JCC), the Project's highest decision-making body. Commitment is also seen at the implementation level, *i.e.*, the Joint Project Management Team (JPMT), which is composed of project managers and staff of the MOPH and NHSO, and JICA experts. JPMT constantly holds meetings for monitoring and technical coordination of the Project's activities. Their members keep a close relationship with each other despite losing the ability to have face-to-face communication under the Work-from-Home policy. Below are three factors that contributed to its success.

Trust: When a member was not able to attend the JPMT meeting, he or she read through the delivered materials and sent comments beforehand. Such a responsible work ethic builds trust in a relationship.

Teamwork: At the planning of activities, we had closer consultation using various communication tools such as e-mail, LINE, and Zoom. In particular, as NHSO is involved with the most activities, their members joined weekly meetings, taking time out from their busy schedules with a team-oriented mindset. At the time of implementation of the activities, both Thailand and Japan provided technical and logistic support.

Common goals: Partnerships are generally made when two parties have a common goal. The Project members share a common goal of promoting UHC in their country and globally as specified in the Project Design Matrix developed based on the discussions and agreement between the two countries. The main premise of the Project is that each member works not for one's own profit but for the good of society.

Achievements

In the past year and a half (2020-2022) amid the COVID-19 pandemic, the regular (at least four times a year) meetings of JPMT and the annual JCC meetings were the main drivers of the Project, keeping it alive and productive. The Project successfully conducted a number of online activities, including twelve technical workshops on health financing, strategic purchasing, health workforce, maternal and child health and UHC Policy Dialogue using Japan and Thailand's experience for other countries in Asia and Africa. Notably, most of these activities were not single events as often seen in the first phase of the Project. Our "new normal" approach led to continuing dialogue between the two countries as well as with participating countries. More importantly, Global Health and UHC Resource Centers have been institutionalized as the asset of the Project (*11,12*). Fruitful learning materials including articles, books, and videos, are readily available to anyone from all over the world.

Conclusion

During the COVID-19 pandemic, driving global health and continuing the UHC momentum at the national level remain important issues. Within the physical constraints borne by COVID-19, the project discovered effective "new normal" approaches especially with coordination of virtual meetings. First, a problem-oriented approach emphasizing practical and interactive discussions on each country's priority issues effectively enhanced mutual learning in South-South and Triangular Cooperation. Second, taking advantage of virtual meetings was useful for maintaining and expanding networks as well as strategically expanding target participants to either side of decision-makers and/or local officers to deepen discussion and facilitate decision-making. Hereon, the maximum use of the existing network is critical. Lastly, our experience also highlighted the significance of commitment, trust, teamwork, and sharing common goals in terms of enhancing partnerships, especially amid the COVID-19 pandemic.

By comparing the above experience with that of other projects between Thailand and Japan, we can identify advantages and disadvantages with each other and work for better management. Our lesson learned is also applicable to other bilateral and multilateral projects in other countries. We believe our experiences and practices will serve as a useful reference to further promote South-South and Triangular cooperation in order to move UHC forward globally.

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

References

1. United Nations Population Fund. South-South and Triangular Cooperation in Action: Sexual and Reproductive Health. *https://lac.unfpa.org/es/publications/south-south-cooperation-action-sexual-and-reproductive-health* (accessed December 17, 2022).
2. United Nations. Goal 17: Revitalize the global partnership for sustainable development. *https://www.un.org/sustainabledevelopment/globalpartnerships* (accessed April 27, 2022).
3. Pan American Health Organization/World Health Organization, United Nations Population Fund, United Nations Children's Fund, United Nations Office for South-South Cooperation. Good Practices in South-South and Triangular Cooperation: Delivering on the Sustainable Development Goal on Good Health and Well-being. *https://www.southsouth-galaxy.org/publications/sdg3-good-practices* (accessed December 17, 2022).
4. The Economic and Social Commission for Asia and the Pacific. South-South Cooperation in Asia and the Pacific –A brief overview. Bangkok, Thailand, 2018. *https://www.unescap.org/sites/default/files/SSC_Paper_v04_20180621_FINAL_formatted.pdf* (accessed December 17, 2022).
5. World Health Organization. Universal Health Coverage. *https://www.who.int/health-topics/universal-health-coverage#tab=tab_1* (accessed April 26, 2022).
6. Task Force on Global Action for Health System Strengthening. G8 Hokkaido Toyako Summit Follow-Up: Global Action for Health System Strengthening Policy: Recommendations to the G8. *http://www.jcie.org/researchpdfs/takemi/full.pdf* (accessed 21 December 17, 2022).
7. Machida M, Miyashita Y. For further collaboration on strengthening Universal Health Coverage (UHC): Partnership project between Japan and Thailand. Glob Health Med. 2021; 3:11-14.
8. Wiederhold BK. Connecting through technology during the coronavirus disease 2019 pandemic: Avoiding "zoom fatigue". Cyberpsychol Behav Soc Netw. 2020; 23:437-438.
9. Oeppen RS, Shaw G, Brennan PA. Human factors recognition at virtual meetings and video conferencing: how to get the best performance from yourself and others. Br J Oral Maxillofac Surg. 2020; 58:643-646.
10. Global Health Division, Office of Permanent Secretary, Thailand Ministry of Public Health. Thailand Global Health Action Plan 2021-2027. *https://tpd.dtam.moph.go.th/images/oic/E-Book/4._GHplanEng_ebook_final.pdf* (accessed December 17, 2022).
11. National Health Security Office. Resource Center Bangkok. *http://eng.nhso.go.th/view/1/Home/EN-US* (accessed June 8, 2022).
12. International Health Policy Program, Thailand,. Resource Center on Global Health and Universal Health Coverage Nonthaburi, Thailand. *https://resourceihpp.com/site/home* (accessed June 8, 2022).

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Specific COVID-19 risk behaviors and the preventive effect of personal protective equipment among healthcare workers in Japan

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Abstract: As coronavirus disease 2019 (COVID-19) outbreaks in healthcare facilities are a serious public health concern, we performed a case-control study to investigate the risk of COVID-19 infection in healthcare workers. We collected data on participants' sociodemographic characteristics, contact behaviors, installation status of personal protective equipment, and polymerase chain reaction testing results. We also collected whole blood and assessed seropositivity using the electrochemiluminescence immunoassay and microneutralization assay. In total, 161 (8.5%) of 1,899 participants were seropositive between August 3 and November 13, 2020. Physical contact (adjusted odds ratio 2.4, 95% confidence interval 1.1-5.6) and aerosol-generating procedures (1.9, 1.1-3.2) were associated with seropositivity. Using goggles (0.2, 0.1-0.5) and N95 masks (0.3, 0.1-0.8) had a preventive effect. Seroprevalence was higher in the outbreak ward (18.6%) than in the COVID-19 dedicated ward (1.4%). Results showed certain specific risk behaviors of COVID-19; proper infection prevention practices reduced these risks.

***Keywords*:** risk factors, seroepidemiology, personal protective equipment

Introduction

Since the World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic in March 2020, data on disease control measures have accumulated (*1-3*) and vaccines have been made

available. However, owing to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and breakthrough infections, COVID-19 is still spreading worldwide in 2022 (*4*). In particular, SARS-CoV-2 infection in nosocomial settings remains a public health concern (*5*). Although guidance on infection prevention strategies for healthcare practices is provided by the state or agency (*6,7*), COVID-19 outbreaks in healthcare facilities continue to occur (*8*). Even after more than two years after the beginning of the pandemic, the spread of the SARS-CoV-2 infection in healthcare facilities is an important issue as it can lead to a shortage of healthcare workers and restrictions on medical care in hospitals. The risk of SARS-CoV-2 infection in healthcare workers needs to be clarified to protect healthcare workers and preserve medical resources.

In Japan, approximately 22 million COVID-19 cases were reported by October 2022 (9). Analyzing the data of the early pandemic period, *i.e.*, the period before the spread of COVID-19 in the community, would be useful for assessing the risk of SARS-CoV-2 infection limited to healthcare facilities.

Front-line healthcare workers are highly exposed to infection through contact with patients with COVID-19; and, they are at an increased risk of infection compared with the general public (*2,3,10*). Previous studies have reported a high seroprevalence of COVID-19 among healthcare workers having direct contact with patients with COVID-19 (*3,11*). Two cohort studies demonstrated that the improper use or lack of personal protective equipment (PPE) was associated with a higher prevalence of COVID-19 (*10,12*). Although face masks reduce the risk of infection (*11,13,14*), evidence on the efficacy of other PPEs and quantitative assessments are limited. Overall, specific risk behaviors for SARS-CoV-2 infection during hospital work are not fully understood.

We conducted this study to investigate COVID-19 risk among healthcare workers in Japan. Additionally, we also explored the differences in seropositivity across diverse occupations not limited to front-line healthcare workers.

Materials and Methods

Study design and participants

We performed a case-control study to evaluate the association between SARS-CoV-2 infection and possible risk factors in nosocomial outbreak settings. We assessed sociodemographic factors, contact history with patients with COVID-19, and PPE use as possible risk factors among staff in seven facilities (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). SARS-CoV-2 infection was defined by a positive result of a serologic test performed using the methods described here. Only participants with both epidemiological information and antibody results available were included. As we focused on the risk in nosocomial settings, participants with contact histories outside their facilities were excluded from the analyses.

Participants were recruited from hospitals where COVID-19 outbreaks occurred between March and August 2020 in Japan (*15*). Not only front-line healthcare workers but also affiliated workers such as cleaning staff were included.

We appointed a representative for each participating hospital, who explained the study outline, benefits, and risks to all staff members. Participation in the study was voluntary and all the participants provided written informed consent. This study was approved by the ethics committee of the National Institute of Infectious Diseases (NIID) (No. 1177) and conducted according to the principles in the Declaration of Helsinki.

Procedures

An identification code was created for each participant, and only anonymized information was shared with the analysis team. The link between the participant's identification code and personal data was managed by the respective hospital representatives.

Blood sampling and questionnaire survey were conducted from August to November 2020 (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The participants were required to provide their epidemiological information on a web-based questionnaire system using their smartphone or computer; the questionnaire comprised the following information: sociodemographic characteristics, underlying medical conditions, occupation, career, details and frequency of contact history with patients with COVID-19, PPE use, and polymerase chain reaction (PCR) results. Information on behavior of each participant during the outbreak period was obtained for data on contact history and PPE use. Data of PCR tests performed at each hospital prior to the serologic test in this study was obtained. The response status was regularly checked, and non-responders were alerted to answer the questions. Each participant was informed of the serologic test result through their personal page in the system. The page was set to be displayed only to the participants who answered the questionnaire so as to improve the completion rate.

The participants were divided into six age groups, each comprising 10 years, ranging from 20s to 70s and over. Their underlying disorders were grouped as immunodeficiency/malignancy and others. Career, defined as the number of years in their occupation, was classified into five groups, in multiples of five. Data on the type of ward was sought for participants whose facilities provided medical treatment for patients with COVID-19, and type of ward was classified as dedicated

COVID-19 ward (ward for the treatment of patients with COVID-19), outbreak ward (non-COVID-19 ward where an outbreak was detected among staff or in-patients), and non-outbreak ward (non-COVID-19 ward where no outbreak was detected among staff or in-patients). Participants who had contact history with patients with COVID-19 were required to provide the details and frequency of their contact (with or without the following actions: entering the room, contact with the surrounding environment, approach within 1 m, conversation, and physical contact). PPE use during treatment of patients with COVID-19 was evaluated as follows: used always, used sometimes, and not used. PPE included surgical masks, gloves, goggles, gowns or aprons, and N95 masks. As the situations where the use of N95 masks was recommended varied by facility, N95 mask use during aerosol-generating procedures was assessed as all participating facilities recommended its use.

Blood samples were collected at each hospital and transported to the NIID in cold chain. We tested for the anti-SARS-CoV-2 antibody using electrochemiluminescence immunoassay (ECLIA, Elecsys® Anti-SARS-CoV-2; Roche Diagnostics K.K., Basel, Switzerland) and microneutralization assay (NIID, Tokyo, Japan). Seropositivity was defined as a positive result for any of these tests, with a cut-off titer of 1.0 for the ECLIA and 1:5 for the microneutralization assay.

The ECLIA was performed on all the samples according to the manufacturer's instructions (*16*). The assay detects antibodies to SARS-CoV-2 nucleocapsid protein, including immunoglobulin G (IgG), using serum or plasma. The test for antibodies to nucleocapsid protein returns positive results in case of the SARS-CoV-2 infection, not the vaccination. The manufacturer has claimed a sensitivity of 99.5% (95% confidence interval [CI]: 88.1-100) based on the test results in symptomatic patients within 14 days post PCR diagnoses. The specificity was evaluated as 99.8% (95% CI: 99.7-99.9) from test results of samples collected before the emergence of SARS-CoV-2 (*16*). The cut-off index of the assay was defined as 1.0 by the manufacturer. The assay was performed as a screening test, and the screening-positivity criterion was set as 0.1 or higher in this study (*17*). Screening-positive cases were evaluated for SARS-CoV-2 microneutralizing antibody using the following method.

The microneutralization assay was developed at the NIID (*18*). Vero E6/TMPRSS2 cells and SARS-CoV-2 JPN/TY/WK-521 strain were used for the assay (*18*). The test serum was diluted in serial two-fold steps from 1:5 to 1:160 and the challenge virus (100 Tissue Culture Infectious Dose 50/50µl) was allowed to react at 37°C for 1 hour. Next, VeroE6/TMPRSS cells were added to the mixture and incubated at 37 °C for 5 days. After the incubation, the cytopathic effect (CPE) of each well was observed under an inverted microscope. The microneutralization titer was evaluated after formalin fixation and crystal violet staining. The highest dilution of wells without CPE was defined as the microneutralization titer.

Statistical analyses

The characteristics of participants with seropositivity were compared using Pearson chi-squared test or Fisher exact test, as appropriate. The outcome of interest was a positive serologic test for SARS-CoV-2, and the possible risk factors were sociodemographic factors, contact history with patients with COVID-19, and PPE use. The risk factors were evaluated using adjusted odds ratios (OR) with 95% CIs using multivariable logistic regression models. Of the significant factors explored using univariable analyses, those affecting the adjusted ORs were included in the final models as possible confounding factors (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The missing values were coded as "no record" and included in the analyses. All analyses were performed using STATA version 15 (StataCorp, College Station, Texas).

Results

A total of 2,059 employees were enrolled in this study (Figure 1). Of these, 124 did not answer the questionnaire, two did not undergo the serologic test, and 34 had contact history with COVID-19-infected persons outside their facility. After excluding these cases, 1,899 participants were included in the analyses.

Participating facilities were distributed in four out of eight regions in Japan (Supplementary Table

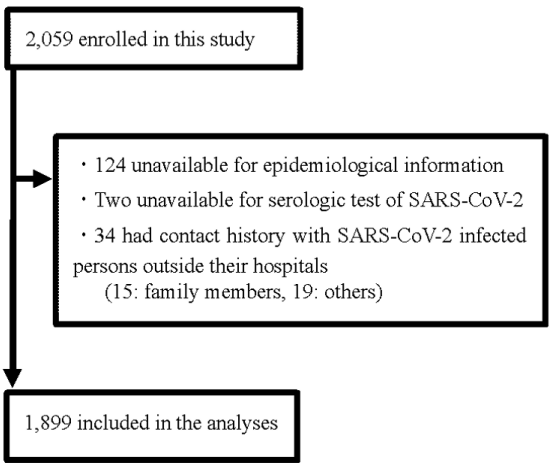

Figure 1. Study flow diagram. We recruited the study participants voluntarily among healthcare workers working at seven hospitals where outbreaks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred between March and August 2020 in Japan. A total of 1,899 participants were included in the analyses, excluding those who were unavailable for epidemiological information or the result of serologic test and those who had contact with SARS-CoV-2 infected persons outside their hospitals.

S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). Three of these facilities had provided medical treatment to COVID-19 patients during each outbreak period. The outbreaks were detected from March to August 2020 and lasted weeks to months (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*).

Blood collection was conducted from August 3 to November 13, 2020, and the period from outbreak to blood sampling was about 2 weeks to 4 months (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The microneutralization assay was performed on 205 samples that screened positive (Table 1). Of these, 140 samples had a microneutralization titer of 1:5 or more, and 21 had an antibody titer of 1 or more on the ECLIA and a microneutralization titer of less than 1:5. A total of 161 samples (8.5%, 95% CI 7.3-9.8) were seropositive. We classified 161 seropositive participants as cases and 1738 seronegative participants as controls. Seropositivity proportion varied by facility, ranging from 24.4% (33 of 135, 95% CI 17.5-32.6) to 1.0% (2 of 196, 95% CI 0.1-3.6; Supplementary

Table 1. Results of the serologic test for severe acute respiratory syndrome coronavirus 2 among healthcare workers in Japan between August and November, 2020

		Total, *n*	Microneutralization titer, *n*					
			< 1:5	1:5	1:10	1:20	1:40	1:80
Antibody titer (ECLIA)	< 0.1	1,694	NA[a]	NA	NA	NA	NA	NA
	≥ 0.1, < 1	46	44	0	2	0	0	0
	≥ 1	159	21	40	47	36	10	5

ECLIA: electrochemiluminescence immunoassay; NA: not applicable; [a]Cases that showed < 0.1 on the ECLIA and were not tested on the microneutralization assay.

Table 2. Sociodemographic characteristics of participants by seropositivity

Variables	All participants, *n* (%)	Seropositive[a], *n* (%)	Seronegative, *n* (%)	*p* value
Sex				0.003
Male	583 (31)	32 (20)	551 (32)	
Female	1,315 (69)	129 (80)	1,186 (68)	
Unknown	1 (0)	0 (0)	1 (0)	
Age group (years)				0.001
≤ 30	609 (32)	72 (45)	537 (31)	
31-40	473 (25)	41 (25)	432 (25)	
41-50	415 (22)	21 (13)	394 (23)	
51-60	270 (14)	14 (9)	256 (15)	
61-70	107 (6)	10 (6)	97 (6)	
≥ 71	25 (1)	3 (2)	22 (1)	
Underlying disorder				0.284
Immunodeficiency or malignancy	33 (2)	3 (2)	30 (2)	
Others	564 (30)	48 (30)	516 (30)	
No underlying disorders	1,260 (66)	103 (64)	1,157 (67)	
Unknown	42 (2)	7 (4)	35 (2)	
Occupation				NA[b]
Office worker	165 (9)	5 (3)	160 (9)	
Doctor	248 (13)	16 (10)	232 (13)	
Nurse	836 (44)	102 (63)	734 (42)	
Nursing assistant	103 (5)	16 (10)	87 (5)	
Rehabilitation staff	105 (6)	7 (4)	98 (6)	
Radiologist	99 (5)	2 (1)	97 (6)	
Pharmacist	39 (2)	1 (1)	38 (2)	
Nutritionist	34 (2)	0 (0)	34 (2)	
Laboratory technician	89 (5)	0 (0)	89 (5)	
Social worker	23 (1)	0 (0)	23 (1)	
Psychologist	3 (0)	0 (0)	3 (0)	
Caregiver	25 (1)	1 (1)	24 (1)	
Cleaning staff	17 (1)	4 (2)	13 (1)	
Others	113 (6)	7 (4)	106 (6)	
Career (years)				0.056
≤ 5	704 (37)	74 (46)	630 (36)	
6-10	412 (22)	38 (24)	374 (22)	
11-20	440 (23)	27 (17)	413 (24)	
21-30	218 (11)	13 (8)	205 (12)	
≥ 31	125 (7)	9 (6)	116 (7)	

NA: not applicable; [a]Seropositive: Microneutralization titer ≥ 5 or antibody titer by ECLIA ≥ 1; [b]The data were too sparse for analysis.

Table 3. Seropositive proportion for severe acute respiratory syndrome coronavirus 2 by sociodemographic factors among healthcare workers in Japan between August and November, 2020

Variables	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR[a]	*p* value
Sex					
Male	5.5 (3.8-7.7)	1 (ref)		1 (ref)	
Female	9.8 (8.3-11.5)	1.9 (1.3-2.8)	0.002	1.3 (0.8-2.1)	0.352
Age group (years)					
≤ 30	11.8 (9.4-14.7)	2.5 (1.5-4.2)	0.000	2.2 (1.2-3.9)	0.011
31-40	8.7 (6.3-11.6)	1.8 (1.0-3.1)	0.037	1.6 (0.8-2.8)	0.156
41-50	5.1 (3.2-7.6)	1 (ref)		1 (ref)	
51-60	5.2 (2.9-8.5)	1.0 (0.5-2.1)	0.942	1.0 (0.5-2.2)	0.970
61-70	9.3 (4.6-16.5)	1.9 (0.9-4.2)	0.100	2.3 (0.9-6.0)	0.095
≥ 71	12.0 (2.5-31.2)	2.6 (0.7-9.2)	0.151	1.4 (0.3-6.5)	0.684
Occupation					
Office worker	3.0 (1.0-6.9)	1 (ref)		1 (ref)	
Doctor	6.5 (3.7-10.3)	2.2 (0.8-6.1)	0.130	5.1 (1.6-15.9)	0.005
Nurse	12.2 (10.1-14.6)	4.4 (1.8-11.1)	0.001	5.4 (2.0-14.6)	0.001
Nursing assistant	15.5 (9.1-24.0)	5.9 (2.1-16.6)	0.001	9.0 (2.9-28.1)	0.000
Rehabilitation staff	6.7 (2.7-13.3)	2.3 (0.7-7.4)	0.168	1.8 (0.5-6.6)	0.346
Radiologist	2.0 (0.2-7.1)	0.7 (0.1-3.5)	0.623	0.8 (0.1-4.3)	0.749
Pharmacist	2.6 (0.1-13.5)	0.8 (0.1-7.4)	0.877	0.7 (0.1-6.9)	0.780
Nutritionist	0 (0-10.3)	NA	NA	NA	NA
Laboratory technician	0 (0-4.1)	NA	NA	NA	NA
Social worker	0 (0-14.8)	NA	NA	NA	NA
Psychologist	0 (0-70.8)	NA	NA	NA	NA
Caregiver	4.0 (0.1-20.4)	1.3 (0.1-11.9)	0.797	1.9 (0.2-19.1)	0.568
Cleaning staff	23.5 (6.8-49.9)	9.8 (2.4-41.2)	0.002	22.7 (3.9-132.0)	0.001
Career (years)					
≤ 5	10.5 (8.3-13.0)	1 (ref)		1 (ref)	
6-10	9.2 (6.6-12.4)	0.9 (0.6-1.3)	0.490	0.7 (0.5-1.2)	0.242
11-20	6.1 (4.1-8.8)	0.6 (0.4-0.9)	0.012	0.8 (0.4-1.4)	0.376
21-30	6.0 (3.2-10.0)	0.5 (0.3-1.0)	0.048	0.9 (0.4-2.0)	0.781
≥ 31	7.2 (3.3-13.2)	0.7 (0.3-1.4)	0.259	1.2 (0.4-3.8)	0.696

CI: confidence interval; OR: odds ratio; NA: not applicable; [a]Adjusted by sex, age, hospital, occupation, and contact history with coronavirus disease 2019 patients.

Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*).

Women accounted for 69.3% (1,315 of 1,899) of the participants and most seropositive cases were also women (80.1%, 129 of 161; Table 2). The number of seropositive participants was the highest for the age group of 20s (44.7%, 72 of 161) and decreased with age. The largest number of participants were nurses (44.0%, 836 of 1,899), followed by doctors (13.1%, 248 of 1,899) and office workers (8.7%, 165 of 1,899). About two-thirds of seropositive participants were nurses (102 of 161, 63.4%), and 9.9% each were doctors (16 of 161) and nursing assistants (16 of 161). None of the nutritionists, laboratory technicians, or social workers had positive serologic tests. The characteristics of underlying disorders and career were similar between seropositive and seronegative participants.

Participants in their 20s had increased odds of seropositivity compared with those in their 40s (aOR 2.2, 95% CI 1.2-3.9: Table 3). The odds of seropositivity in doctors (aOR 5.1, 95% CI 1.6-15.9), nurses (aOR 5.4, 95% CI 2.0-14.6), nursing assistants (aOR 9.0, 95% CI 2.9-28.1), and cleaning staff (aOR 22.7, 95% CI 3.9-132.0) were higher than those among office workers. Seropositivity odds were not higher in women than in men. We could not find any association between career and seropositivity after controlling for confounders.

Having contact history with COVID-19 patients was associated with seropositivity (aOR 4.8, 95% CI 2.8-8.1; Table 4). The group with physical contact with COVID-19 patients had a higher seropositive proportion than the group without it (aOR 2.4, 95% CI 1.1-5.6). The seropositivity of the participants who performed aerosol-generating procedures for COVID-19 patients was higher than those who did not (aOR 1.9, 95% CI 1.1-3.2; Table 5). No association was found between other contact histories and seropositivity (Table 4). Total number of contact days and average contact time per day were analyzed for contact frequency with COVID-19 patients, but we did not find any association between these factors and COVID-19 infection.

Participants who used goggles all the time during medical procedures (aOR 0.2, 95% CI 0.1-0.5; Table 5), and those who used them occasionally (aOR 0.5, 95% CI 0.2-1.0), were less infected than those who did not. No association was found between infection and the use of surgical masks, gloves, and gowns, regardless of their frequency of use. The group who always used N95

Table 4. Seropositive proportion for severe acute respiratory syndrome coronavirus 2 by contact history with coronavirus disease 2019 patients among healthcare workers in Japan between August and November, 2020

Variables	Number of seropositive participants	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR	*p* value
Any contact history with COVID-19 patients[a]						
Yes	125/1,011	12.4 (10.4-14.6)	5.3 (3.3-8.5)	0.000	4.8 (2.8-8.1)	0.000
No	20/768	2.6 (1.6-4.0)	1 (ref)		1 (ref)	
The following analyses are among the participants who had any contact history with COVID-19 patients.						
(Details of contact history[b])						
Entering the room						
Yes	105/733	14.3 (11.9-17.1)	2.9 (1.6-5.3)	0.000	0.8 (0.3-2.0)	0.647
No	13/239	5.4 (2.9-9.1)	1 (ref)		1 (ref)	
Contact with the surrounding environment						
Yes	101/660	15.3 (12.6-18.3)	3.5 (2.0-6.1)	0.000	1.0 (0.4-2.3)	0.937
No	15/304	4.9 (2.8-8.0)	1 (ref)		1 (ref)	
Approach within 1m						
Yes	115/875	13.1 (11.0-15.6)	3.4 (1.2-9.3)	0.020	1.8 (0.5-5.9)	0.356
No	4/93	4.3 (1.2-10.6)	1 (ref)		1 (ref)	
Conversation						
Yes	111/819	13.6 (11.3-16.1)	3.2 (1.5-7.1)	0.003	2.5 (1.0-6.4)	0.051
No	7/151	4.6 (1.9-9.3)	1 (ref)		1 (ref)	
Physical contact						
Yes	104/648	16.0 (13.3-19.1)	3.5 (2.1-6.0)	0.000	2.4 (1.1-5.6)	0.037
No	17/331	5.1 (3.0-8.1)	1 (ref)		1 (ref)	
(Frequency of contact history[a])						
Total days of contact						
≤ 3	28/356	7.9 (5.3-11.2)	1 (ref)		1 (ref)	
4-7	24/156	15.4 (10.1-22.0)	2.1 (1.2-3.8)	0.011	1.4 (0.7-2.7)	0.307
8-14	21/122	17.2 (11.0-25.1)	2.4 (1.3-4.5)	0.004	1.5 (0.8-3.0)	0.237
15-30	23/132	17.4 (11.4-25.0)	2.5 (1.4-4.5)	0.003	1.7 (0.9-3.3)	0.131
≥ 31	20/182	11.0 (6.8-16.5)	1.4 (0.8-2.6)	0.231	1.0 (0.5-2.1)	0.900
Average time of contact per day						
< 15min	23/327	7.0 (4.5-10.4)	1 (ref)		1 (ref)	
≥ 15min, < 1H	30/308	9.7 (6.7-13.6)	1.4 (0.8-2.5)	0.220	1.0 (0.5-1.9)	0.969
≥ 1H, < 2H	21/121	17.4 (11.1-25.3)	2.8 (1.5-5.2)	0.002	1.3 (0.6-2.6)	0.546
≥ 2H	48/206	23.3 (17.7-29.7)	4.0 (2.4-6.8)	0.000	1.5 (0.8-2.8)	0.251

CI: confidence interval; OR: odds ratio; COVID-19: coronavirus disease 2019; [a]Adjusted by sex, age, hospital, and occupation; [b]Adjusted by sex, age, hospital, occupation, entering the room, contact with the surrounding environment, approach within 1m, conversation, and physical contact.

masks during the aerosol-generating procedure had a lower seropositive proportion than the group who did not use them (aOR 0.3, 95% CI 0.1-0.8). No association was found between the group who used N95 masks occasionally and SARS-CoV-2 infection.

Only one of 71 workers in the COVID-19 ward was seropositive (seropositivity proportion 1.4%, 95% CI 0.04-7.6), while 35 of 188 were positive in the outbreak ward (18.6%, 95% CI 13.3-24.9; Figure 2). The seropositivity proportion in the non-outbreak ward (1.4%, 95% CI 0.6-2.9) was similar to that in the COVID-19 ward.

PCR results prior to the serologic test were obtained for 965 of 1,899 participants (Supplementary Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). When both positive and negative PCR results were reported, the analyses were performed using positive results. Of the 121 participants who reported PCR positive results, 23 were seronegative. The duration from PCR to serologic test ranged from 96 to 192 days.

Discussion

This study revealed certain risk behaviors for SARS-CoV-2 infection in nosocomial settings: physical contact and aerosol-generating procedures with patients with COVID-19. Doctors, nurses, and nursing assistants whose work involved such risk behaviors were more infected than office workers. Among occupations not involving patient-care, cleaning staff had a high seroprevalence; therefore, infection prevention measures for this employee group are also important. Of the PPE, goggles and N95 masks prevented SARS-CoV-2 infection with dose-response relationships.

The total seroprevalence in participants in this study (8.5%, 95% CI 7.3-9.8; 161 of 1,899) was much higher than that in the general population in Japan (0.7%, 103 of 15,043), according to a survey conducted several months after our study (*20*). As such, the study was conducted at a time when the infection was not widespread in the community and was appropriate for assessing the risk of infection in health care institutions.

Table 5. Preventive effect of severe acute respiratory syndrome coronavirus 2 infection by using personal protective equipment among healthcare workers in Japan between August and November, 2020

Variables	Number of seropositive participants	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR	*p* value
Any medical procedures for COVID-19 patients[a]						
Yes	94/607	15.5 (12.7-18.6)	2.1 (1.3-3.3)	0.001	1.5 (0.8-2.5)	0.170
No	27/337	8.0 (5.3-11.4)	1 (ref)		1 (ref)	
The following analyses[b] are among participants who performed any medical procedures for COVID-19 patients.						
Surgical masks use						
Always	86/539	16.0 (13.0-19.3)	1.6 (0.6-4.1)	0.365	1.0 (0.3-3.1)	0.993
Sometimes	3/21	14.3 (3.0-36.3)	1.4 (0.3-6.3)	0.690	0.9 (0.1-5.7)	0.918
Never	5/46	10.9 (3.6-23.6)	1 (ref)		1 (ref)	
Gloves use						
Always	62/466	13.3 (10.4-16.7)	0.5 (0.2-1.1)	0.069	0.5 (0.1-1.8)	0.302
Sometimes	23/103	22.3 (14.7-31.6)	0.9 (0.4-2.2)	0.804	0.6 (0.2-2.0)	0.384
Never	9/37	24.3 (11.8-41.2)	1 (ref)		1 (ref)	
Goggles use						
Always	39/363	10.7 (7.8-14.4)	0.4 (0.2-0.7)	0.001	0.2 (0.1-0.5)	0.000
Sometimes	28/124	22.6 (15.6-31.0)	1.0 (0.5-1.8)	0.956	0.5 (0.2-1.0)	0.041
Never	27/118	22.9 (15.7-31.5)	1 (ref)		1 (ref)	
Gowns or aprons use						
Always	53/396	13.4 (10.2-17.1)	0.7 (0.4-1.4)	0.320	1.5 (0.5-4.9)	0.483
Sometimes	28/135	20.7 (14.2-28.6)	1.2 (0.6-2.5)	0.612	1.4 (0.5-4.0)	0.537
Never	13/73	17.8 (9.8-28.5)	1 (ref)		1 (ref)	
Aerosol-generating procedures for COVID-19 patients[a]						
Yes	43/221	19.5 (14.5-25.3)	2.7 (1.7-4.1)	0.000	1.9 (1.1-3.2)	0.021
No	57/689	8.3 (6.3-10.6)	1 (ref)		1 (ref)	
The following analysis is among participants who performed aerosol-generating procedures for COVID-19 patients.						
N95 masks use[a]						
Always	22/153	14.4 (9.2-21.0)	0.3 (0.2-0.8)	0.008	0.3 (0.1-0.8)	0.022
Sometimes	6/23	26.1 (10.2-48.4)	0.7 (0.2-2.3)	0.586	0.5 (0.1-2.1)	0.321
Never	14/43	32.6 (19.1-48.5)	1 (ref)		1 (ref)	

CI: confidence interval; OR: odds ratio; COVID-19: coronavirus disease 2019; [a]Adjusted by sex, age, hospital, and occupation; [b]Adjusted by sex, age, hospital, occupation, and eye shield use.

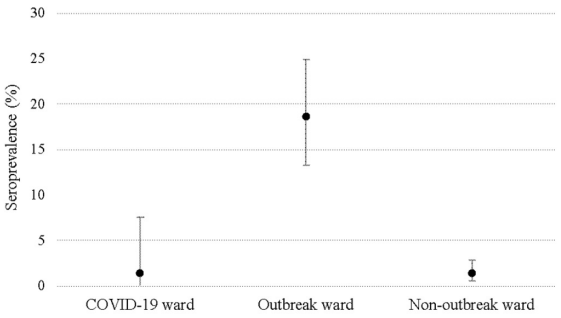

Figure 2. COVID-19 seroprevalence by ward type among healthcare workers in Japan between August and November, 2020. The wards were classified as COVID-19 ward (ward for the treatment of COVID-19 patients), outbreak ward (non-COVID-19 ward where outbreak was detected among staff or in-patients), and non-outbreak ward (non-COVID-19 ward where outbreak was not detected among staff or in-patients). The point estimates (dots) and 95% confidence intervals (lines) of COVID-19 seroprevalence are shown. The COVID-19 ward had the lower seroprevalence than the outbreak ward and similar to the non-outbreak ward.

So far, healthcare workers with patient contact had been reported to have high seropositivity (*3,11,13,21,22*). Our study also showed that doctors, nurses, and nursing assistants, *i.e.*, those who are engaged in patient care, were more infected than office workers. Rehabilitation staff, radiologists, and caregivers also had contact with patients, but they were not more infected than office workers. These results might reflect that they had a lesser chance of being included in risk behaviors such as aerosol-generating procedures. There were no seropositive participants among nutritionists, laboratory technicians, social workers, and psychologists. Similar to our study, fewer instances of infection in laboratory technicians were reported in previous studies (*2,23*), and the risk of infection from specimens obtained from patients with COVID-19 was low.

Cleaning staff showed a high seropositivity in our study. One case series also reported SARS-CoV-2 infection in cleaning staff who had no contact with patients with COVID-19 (*24*). Of the eight infected cleaners in the study, only one wore a face shield and had limited opportunities for infection prevention and control (IPC) training (*24*). In another observational study, cleaning staff had the highest seropositivity among staff working in hospitals with COVID-19 outbreaks (*23*). Of the 17 cleaning staff members who participated in our study, none reported a history of contact with patients with COVID-19. Two of the four cleaners who were seropositive had not undergone PCR testing during

the outbreak period as they were not suspected to have SARS-CoV-2 infection by epidemiological investigation. Transmission by inhalation of infected aerosols in areas with patients with COVID-19 or through contact with contaminated fomites was suspected (*25*). Cleaning staff might be less trained in infection control than frontline healthcare workers and it is important to strengthen IPC training for them.

Healthcare workers in their 20s were more infected than those in their 40s. The susceptibility to SARS-CoV-2 infection by age group during the pre-vaccination period has been previously discussed. One systematic review and meta-analysis about household transmission of SARS-CoV-2 reported the secondary infection rate in family members with patients with COVID-19 to be low in children and high in older adults (*26*). In addition, population-based seroepidemiological surveys showed that children were less infected than adults, and the point estimates of seropositivity rates in people in their 40s and 50s were higher than those in other generations (*22,27*). We could not find reports of young adults being more susceptible to infection in the general population. Healthcare workers, meanwhile, have been reported to be more infected in the younger age group, similar to our study (*2,3*). Healthcare workers in their 20s might have more close contact with patients with COVID-19 than those in their 40s and 50s, and they might be unfamiliar with PPE use.

Physical contact with patients with COVID-19, the closest form of contact in our questionnaire, was considered a risk behavior for SARS-CoV-2 infection. The association between other contact behaviors with patients with COVID-19 (entering the room, contact with the surrounding environment, approach within 1 m, conversation) and seropositivity was unclear, but the point estimates of OR tended to be higher for closer contact.

The group that always used N95 masks during aerosol-generating procedures was found to be less infected, which was consistent with previous studies (*1,3,13*). However, there was no conclusive result on the association between surgical masks use and SARS-CoV-2 infection in our study. As N95 masks users were trained rigorously on the use of PPE, they might have been able to ensure appropriate fitting of their masks. However, surgical masks were worn by diverse hospital staff, and some participants might have been unfamiliar with wearing them correctly. In addition, some participants reported a lack of PPE during the study period. The preventive effect of surgical masks may have been underestimated owing to their improper wear or reuse. Among other PPE, the use of goggles prevented SARS-CoV-2 infection with dose-response relationships.

The outbreak ward had the highest seroprevalence in this study, and the COVID-19 ward had as few infections as the non-outbreak ward. By facility, seropositivity proportions were the highest in facilities that did not treat patients with COVID-19 during the study period. A questionnaire survey conducted in Japan from July to September 2021 also reported nosocomial outbreaks in facilities that did not provide COVID-19 inpatient care (*8*). The high seroprevalence in facilities that did not treat patients with COVID-19 suggests that viral transmission seemed to occur from an undiagnosed SARS-CoV-2-infected person with incomplete PPE use. In addition, the low seroprevalence in the COVID-19 ward indicated that risk factors could be modified with appropriate infection prevention.

In the 23 participants who previously tested positive by PCR and negative for serologic testing, the shortest duration from PCR to serologic test was 96 days. IgG for SARS-CoV-2 were produced approximately 2 weeks after infection (*28,29*). Therefore, the negative serologic results were not due to early testing. Longitudinal antibody responses against SARS-CoV-2 are under discussion. Some studies reported that neutralizing antibodies against SARS-CoV-2 had declined within a few months after disease onset (*30*), whereas others reported them to last for months to half a year (*31-33*). All 17 participants who reported the PCR test date had an interval of more than 3 months from the PCR to the antibody test, and 13 had more than half a year (median 184 days, range 96-192 days). This group might include those who had seroconverted, but the value decreased by the time the serologic test was conducted.

Multiple variants of SARS-CoV-2 have been reported during this pandemic. This study assessed the risk of wild-type virus infection, and the strength of the association between each risk factor and infection may not be consistent in the current epidemic of SARS-CoV-2 variants. However, quantitative risk assessments including a control group were limited in Japan, and the results of this study would be useful as fundamental data for future pandemics caused by strains with different infectivity.

This study has several strengths. First, we evaluated the SARS-CoV-2 infection through seroprevalence using a robust method. ECLIA was performed for screening in all cases, and the positivity criteria were set lower than the manufacturer's criteria so that false negatives were excluded. The screening-positive cases were tested using a microneutralization assay with high sensitivity and specificity. Second, we collected epidemiological information through a web-based system. As we were able to check the real-time response status, a high response rate (1,935 out of 2,059, 94.0%) could be obtained by sending appropriate reminders. Third, we recruited study participants regardless of prior PCR results. People with positive PCR results would be more concerned about the contexts in which they became infected than those who had negative PCR results or had not performed PCR. Therefore, we were able to minimize recall bias. Finally, as there were only

a few community-acquired SARS-CoV-2 infections during our study period, we were able to assess the risk of infection limited to each healthcare facility.

Our study has several limitations. As this was a case-control study, causality could not be discussed. We could only show the strength of associations between SARS-CoV-2 infection and possible risk factors. However, the risk behaviors associated with SARS-CoV-2 infection in our study were consistent with other research methods such as cohort studies, systematic reviews, and meta-analyses (*2,3,11-13,34,35*). In addition, a dose-response relationship was found in the preventive effect of the use of goggles, which suggested a causal relationship. Second, wearing of PPE by patients with COVID-19 in contact with the participants seems to be a possible confounding factor, but we could not adjust this factor as we did not seek this information. Third, we could not exclude selection bias because we employed voluntary participation. Those with prior positive PCR results might have been more likely to not participate in the study than those who had negative results or were untested. Therefore, the seropositivity rate might be underestimated. However, it is unclear whether this bias raises or lowers the odds of risk behaviors. As information was collected through a self-reported questionnaire, recall bias could have occurred. Social desirability bias might influence the responses, especially with regard to PPE use. We tried to mitigate these information biases by communicating the serologic test result after questionnaire completion.

In conclusion, we investigated specific risk behaviors in nosocomial settings and the preventive effect of each PPE with a quantitative assessment. The differences in seropositivity rates by ward type suggested that these risk factors can be modified through appropriate infection prevention measures. COVID-19 outbreaks in hospitals which affect medical resources still remained a public health concern in 2022. Nonpharmaceutical intervention with proper PPE use remains critically important, especially for populations with inadequate IPC training.

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References

1. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: A systematic review and meta-analysis. Lancet. 2020; 395:1973-1987.
2. Iversen K, Bundgaard H, Hasselbalch RB, *et al.* Risk of COVID-19 in health-care workers in Denmark: An observational cohort study. Lancet Infect Dis. 2020; 20:1401-1408.
3. Sims MD, Maine GN, Childers KL, Podolsky RH, Voss DR, Berkiw-Scenna N, Oh J, Heinrich KE, Keil H, Kennedy RH, Homayouni R. Coronavirus disease 2019 (COVID-19) seropositivity and asymptomatic rates in healthcare workers are associated with job function and masking. Clin Infect Dis. 2021; 73:S154-S162.
4. World Health Organization. COVID-19 Weekly Epidemiological Update. *https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---6-july-2022* (accessed July 11, 2022).
5. Tokyo Metropolitan Infectious Disease Surveillance Center. Number of cases by location of COVID-19 cluster. *http://idsc.tokyo-eiken.go.jp/diseases/2019-ncov/* (accessed December 28, 2022).
6. National Institute of Infectious Diseases. Infection control measures for COVID-19. *https://www.niid.go.jp/niid/images/epi/corona/2019nCoV-01-200602tbl.pdf* (accessed October 2, 2022).
7. World Health Organization. Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed. *https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-2021.1* (accessed December 31, 2022).
8. The Japanese Association for Infectious Diseases. The 3rd COVID-19 Nosocomial Infection Questionnaire Survey. *https://www.kansensho.or.jp/modules/news/index.php?content_id=318* (accessed December 28, 2022). (in Japanese)
9. Ministry of Health, Labor and Welfare. COVID-19 information. *https://covid19.mhlw.go.jp/en/* (accessed November 2, 2022).
10. Nguyen LH, Drew DA, Graham MS, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: A prospective cohort study. Lancet Public Health. 2020; 5:e475-e483.
11. Chen Y, Tong X, Wang J, Huang W, Yin S, Huang R, Yang H, Chen Y, Huang A, Liu Y, Chen Y, Yuan L, Yan X, Shen H, Wu C. High SARS-CoV-2 antibody prevalence among healthcare workers exposed to COVID-19 patients. J Infect. 2020; 81:420-426.
12. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk factors of healthcare workers with coronavirus disease 2019: A retrospective cohort study in a designated hospital of Wuhan in China. Clin Infect Dis. 2020; 71:2218-2221.
13. Martischang R, Iten A, Arm I, Abbas M, Meyer B, Yerly S,

Eckerle I, Pralong J, Sauser J, Suard JC, Kaiser L, Pittet D, Harbarth S. Severe acute respiratory coronavirus virus 2 (SARS-CoV-2) seroconversion and occupational exposure of employees at a Swiss university hospital: a large longitudinal cohort study. Infect Control Hosp Epidemiol. 2022; 43:326-333.
14. Kwon S, Joshi AD, Lo CH, *et al.* Association of social distancing and face mask use with risk of COVID-19. Nat Commun. 2021; 12:3737.
15. Kato H, Seki K, Maeda Y, Noda Y, Iinuma Y, Kitaoka M, Kiso K, Koshida R, Kurosu H, Yamagishi T, Shimada T, Suzuki M, Sunagawa T. Rapid response to a coronavirus disease 2019 (COVID-19) outbreak in a psychiatry hospital-Kanazawa City, Japan, March to April 2020. Antimicrob Steward Healthc Epidemiol. 2022; 2:e57.
16. Roche Diagnostics K.K. Elecsys® Anti-SARS-CoV-2 RUO. *https://diagnostics.roche.com/jp/ja/products/params/elecsys-anti-sars-cov-2.html* (accessed August 6, 2022). (in Japanese)
17. Public Health England. Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays. *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898437/Evaluation__of_sensitivity_and_specificity_of_4_commercially_available_SARS-CoV-2_antibody_immunoassays.pdf* (accessed March 28, 2022).
18. Ministry of Health, Labor and Welfare. Testing procedure of National Epidemiological Surveillance of Vaccine-Preventable Diseases. *https://www.niid.go.jp/niid/images/epi/yosoku/AnnReport/2021-99.pdf* (accessed August 10, 2022). (in Japanese)
19. Matsuyama S, Nao N, Shirato K, *et al.* Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A. 2020; 117:7001-7003.
20. Ministry of Health, Labor and Welfare. The seroprevalence of SARS-CoV-2 in general public. *https://www.mhlw.go.jp/content/000761671.pdf* (accessed January 26, 2022). (in Japanese)
21. Korth J, Wilde B, Dolff S, Anastasiou OE, Krawczyk A, Jahn M, Cordes S, Ross B, Esser S, Lindemann M, Kribben A, Dittmer U, Witzke O, Herrmann A. SARS-CoV-2-specific antibody detection in healthcare workers in Germany with direct contact to COVID-19 patients. J Clin Virol. 2020; 128:104437.
22. Chen X, Chen Z, Azman AS, Deng X, Sun R, Zhao Z, Zheng N, Chen X, Lu W, Zhuang T, Yang J, Viboud C, Ajelli M, Leung DT, Yu H. Serological evidence of human infection with SARS-CoV-2: A systematic review and meta-analysis. Lancet Glob Health. 2021; 9:e598-609.
23. Alkurt G, Murt A, Aydin Z, *et al.* Seroprevalence of coronavirus disease 2019 (COVID-19) among health care workers from three pandemic hospitals of Turkey. PLoS One. 2021; 16:e0247865.
24. Kurosu H, Watanabe K, Kurosawa K, *et al.* Possible contact transmission of SARS-CoV-2 in healthcare settings in Japan, 2020-2021. Infect Control Hosp Epidemiol. 2022; 43:1296-1298.
25. Centers for Disease Control and Prevention. Science Brief: SARS-CoV-2 and surface (fomite) transmission for indoor community environments. *https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html* (accessed March 30, 2022).
26. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: A systematic review and meta-analysis. JAMA Netw Open. 2020; 3:e2031756.
27. Le Vu S, Jones G, Anna F, *et al.* Prevalence of SARS-CoV-2 antibodies in France: Results from nationwide serological surveillance. Nat Commun. 2021; 12:3025.
28. Borremans B, Gamble A, Prager KC, Helman SK, McClain AM, Cox C, Savage V, Lloyd-Smith JO. Quantifying antibody kinetics and RNA detection during early-phase SARS-CoV-2 infection by time since symptom onset. Elife. 2020; 9:e60122.
29. Altawalah H. Antibody responses to natural SARS-CoV-2 infection or after COVID-19 vaccination. Vaccines. 2021; 9:910.
30. Marot S, Malet I, Leducq V, *et al.* Rapid decline of neutralizing antibodies against SARS-CoV-2 among infected healthcare workers. Nat Commun. 2021; 12:844.
31. Yamayoshi S, Yasuhara A, Ito M, *et al.* Antibody titers against SARS-CoV-2 decline, but do not disappear for several months. EClinicalMedicine. 2021; 32:100734.
32. Goto A, Go H, Miyakawa K, *et al.* Sustained neutralizing antibodies 6 months following infection in 376 Japanese COVID-19 survivors. Front Microbiol. 2021; 12:661187.
33. Gudbjartsson DF, Norddahl GL, Melsted P, *et al.* Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med. 2020; 383:1724-1734.
34. Gómez-Ochoa SA, Franco OH, Rojas LZ, Raguindin PF, Roa-Díaz ZM, Wyssmann BM, Guevara SLR, Echeverría LE, Glisic M, Muka T. COVID-19 in health-care workers: A living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes. Am J Epidemiol. 2021; 190:161-175.
35. Gholami M, Fawad I, Shadan S, Rowaiee R, Ghanem H, Khamis AH, Ho SB. COVID-19 and healthcare workers: A systematic review and meta-analysis. Int J Infect Dis. 2021; 104:335-346.

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Prevalence of and factors associated with diabetes mellitus among people living with HIV in Vietnam

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Abstract: Studies have shown that people living with HIV (PLWH) have a higher risk of having non-communicable diseases (NCDs) than do people without HIV. In Vietnam, HIV remains a major public health concern, and with recent rapid economic growth, NCDs such as diabetes mellitus (DM) have become a significant disease burden. This cross-sectional study was conducted to examine the prevalence of DM and the factors associated with DM among PLWH on antiretroviral therapy (ART). In total, 1,212 PLWH were included in the study. The age-standardized prevalence of DM and pre-diabetes were 9.29% and 10.32%, respectively. In the multivariate logistic regression analysis, male sex, age above 50 years, and body mass index ≥ 25 kg/m^2 were associated with DM, and borderline p-value was found for associations with current smoking and years on ART. The results suggest higher DM prevalence among PLWH and that longer time on ART could be an important risk factor for DM among PLWH. These findings also suggest that interventions such as weight control and smoking cessation support could be provided at outpatient clinics. Integration of HIV/AIDS and NCDs services is essential to address health needs comprehensively and enhance health-related quality of life for PLWH.

***Keywords*:** non-communicable disease, communicable disease, low- middle-income countries

Introduction

Recent advances in antiretroviral therapy (ART) have improved the life expectancy of people living with HIV (PLWH), and the global HIV population is both aging and increasing. Aging increases comorbidity; therefore non-communicable diseases (NCDs) are posing new public health problems for PLWH in low- and middle-income countries (LMICs) (*1*). Studies have shown that because of HIV infection and treatment toxicity, PLWH have a higher risk of having NCDs such as cardiovascular disease (CVD), diabetes mellitus (DM), and non-AIDS-related cancers compared to people without HIV (*2-4*).

The burden of disease from DM has become significant in Vietnam. According to the International Diabetes Federation, the prevalence of DM was 6.1% in 2021, and was projected to reach 7.1% by 2045 (*5*). Vietnam has experienced rapid economic growth and urbanization since the Doi-Moi policy (transitioning to a market economy) was introduced in 1986. There is a concern that traditional risk factors such as smoking, poor diet, and a sedentary lifestyle could be more prevalent because of these social and demographic changes (*6*), further leading to increased prevalence of DM in the future.

The HIV epidemic remains a major public health problem in Vietnam. While AIDS-related mortality and new infections have declined in recent decades, the percentage of PLWH aged 50 years and above has been increasing (*7,8*). In addition, excess alcohol intake and smoking are known risk factors for DM (*9,10*), and those factors were more prevalent among PLWH than in the general population (*11,12*). Therefore, it is essential to understand the magnitude of the DM burden among PLWH in Vietnam.

Prevalence data on DM is vital for medical decision-making and the appropriate allocation of healthcare resources. Nonetheless, very few studies have investigated DM prevalence among PLWH in Vietnam. According to a literature review using PubMed, Web of Science, Cochrane library, and Global Health with keywords of diabetes AND Vietnam AND HIV, two studies were found, which investigated DM among PLWH in the Asian- Pacific region including Vietnam. However, no study focused on PLWH in Vietnam for DM prevalence. In addition, it is important to understand factors associated with DM to design an effective

strategy. Several studies have investigated factors associated with DM among PLWH in LMICs. However, most of these were conducted in Sub-Saharan Africa, with only a few conducted in the Asian-Pacific region (*13*). Because DM is associated with lifestyle factors, contextual differences may influence the onset of DM among PLWH. Moreover, the investigated factors and reported results have varied across studies (*13-16*). Few studies have examined HIV-related and traditional factors simultaneously, including lifestyle factors such as dietary patterns and physical exercise, to explore which factors are more likely to affect NCDs among PLWH.

Therefore, to overcome these limitations of past studies, we conducted the present study to examine the prevalence of DM among PLWH on ART and investigate the associations between DM and traditional and HIV-related factors.

Methods

Study design and participants

This study employed a cross-sectional design and recruited PLWH in a hospital-based cohort, the Hanoi cohort, at the National Hospital for Tropical Diseases (NHTD) in Hanoi, Vietnam. Inclusion criteria for the Hanoi cohort were: *i*) aged 18 and above, *ii*) on ART at NHTD, *iii*) provide written consent for study participation. Participants were excluded if physicians deemed them inappropriate to participate in the study. NHTD is a central hospital specializing in infectious diseases that has one of the largest HIV outpatient clinics in Vietnam. In the cohort, clinical data were prospectively collected every six months under the Japan Initiative for Global Research Network on Infectious Diseases (2006-2018) and the Science and Technology Research Partnership for Sustainable Development (SATREPS, 2019-present) programs. For the cross-sectional study, relevant clinical data was obtained from the database of the cohort, and a self-reported questionnaire survey on lifestyles and blood glucose testing were conducted between December 2020 and January 2021. The study protocol was approved by the Human Research Ethics Committee of NHTD (No:15/ HDDD-NDTU). All study participants provided a written informed consent for participation and for the use and publication of their clinical and laboratory data for research. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Measurements

DM case identification

Fasting plasma glucose was measured using the Roche Cobas 6000 analyzer (Roche Molecular Diagnostics, Pleasanton, CA). Based on World Health Organization (WHO) diagnostic criteria, participants were considered to have DM if plasma glucose was ≥ 7.0 mmol/L without DM treatment or if participants had a history of DM diagnosis. Pre-diabetes was identified if 6.1 mmol/L ≤ plasma glucose < 7.0 mmol/L without DM treatment and previous DM diagnosis (*17*).

Traditional factors

The questionnaire recorded the following sociodemographic and traditional factors: sex, age, occupation, monthly household income, exercise intensity level, smoking, alcohol drinking, fruit intake, and vegetable intake. Age was divided into four groups: < 40 years, 40-49 years, 50-59 years, and 60 years and above. Occupation was categorized as government employee, non-government employee, farmer, self-employed, student, and unemployed. Monthly household income was divided into four categories: < 4,000,000 Vietnamese dong (VND), 4,000,000-7,999,999 VND, 8,000,000 VND and more, and unknown. Exercise intensity level was measured by the International Physical Activity Questionnaire (IPAQ) (*18*). According to the guideline, the metabolic equivalent task (MET)-minutes per week of each activity (vigorous-intensity activity, moderate-intensity activity, and walking) was calculated and classified into one of three categories: low, moderate, and high. Data on smoking, alcohol drinking, and fruit and vegetable intake were collected based on the WHO STEPS surveillance questionnaire (*19*). Participants were considered current smokers if they answered smoking either daily or less than daily, and current alcohol drinkers if they answered they had had alcohol drinks in the last 12 months. Bodyweight was measured when the questionnaire was administered, and body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Participants with a BMI ≥ $25kg/m^2$ were classified as overweight/obese.

HIV-related factors

The following data on HIV-related factors were collected from the Hanoi cohort database: latest CD4 counts (/μl), latest plasma viral load (pVL) (copies/ml), years since HIV diagnosis, years on ART, and duration of didanosine (ddI), stavudine (d4T), and lopinavir/ritonavir (LPV/r) exposure. Exposure to LPV/r, ddI and d4T were selected because several studies have reported that the use of protease inhibitors and nucleoside reverse transcriptase inhibitors increases the risk of hyperglycemia or DM (*20-22*).

Statistical analysis

The overall prevalence of DM and pre-diabetes were calculated by standardizing according to the age distribution of the National Survey on the Risk Factors

of Non-Communicable Diseases (STEPS) Vietnam 2015 (*23*). The direct standardization method was used. To match the age distribution, study participants aged 70 years and above were excluded when standardization was performed.

Given the exploratory nature of this study, the cut-offs were chosen for fruit intake, vegetable intake, years since HIV diagnosis, years on ART, and duration of ddI, d4T, and LPV/r exposure based on visual analysis of DM case distribution using histograms. Because few DM cases have been exposed to ddI, exposure to ddI and d4T were merged into one category, *i.e*., duration of ddI or d4T exposure. Fruit intake and vegetable intake were grouped into two categories: consume every day and less than every day. The latest CD4 count and pVL were divided into two categories: < 200 and 200 and above. Years since HIV diagnosis and years on ART were divided into two categories: < 11 years and 11 years and above. Duration of ddI or d4T exposure and duration of LPV/r exposure were divided into the following categories: < 3 years and 3 years and above; < 7 years and 7 years and above, respectively.

Associations between DM and traditional and HIV-related factors were explored in a univariate logistic regression analysis. Variables that were significant for the univariate analysis ($p < 0.1$) were included in the multivariate analysis. Before the variables to be included in multivariate analysis were identified, Spearman's correlation coefficient was calculated. If the coefficient was 0.6 or higher, variables were excluded from the multivariate analysis to avoid multicollinearity. Two multivariate models were adopted to explore the impacts of traditional factors on DM before and after adjustment for HIV-related factors. Model 1 includes traditional factors; model 2 includes traditional and HIV-related factors.

To minimize selection bias, multivariate imputation using chained equations was used to calculate values of the missing variables. The number of missing values ranged from 0 to 11.86% for any single variable. All statistical analysis was performed using Stata software (version 16, StataCorp LLC, College Station, TX).

Results

Since October 2007, a total of 2,198 patients had registered for the Hanoi cohort, and 1,225 were followed up in December 2020 and January 2021. Of those, 13 were excluded from the analyses: 11 who did not receive blood tests because of time limitations, and two who did not answer more than half of the questions on the questionnaire. The analysis therefore included data from 1,212 PLWH.

Baseline characteristics

Baseline characteristics are shown in Table 1. The mean age was 43.8 years, and 57.34% of the participants were men. Age-standardization did not greatly change mean age (mean age after exclusion of those aged 70 and above = 43.35 years). Approximately half of participants were self-employed (43.32%), followed by farmers (20.0%). Approximately one-fourth of participants' monthly household income was below 4,000,000 VND (approx. 177 USD) per month. The mean body weight and BMI were 57.56 kg and 21.92, respectively. The mean number of years since ART initiation was 10.25, and the mean of the latest CD4 count was 549.5. Most participants (99.26%) achieved a viral load below 200 copies/ml. The percentage of those exposed to LPV/r for 7 years and above was 8.25%, and 12.54% had been exposed to either ddI or d4T for 3 years or more.

Prevalence of DM and pre-diabetes

Among the participants, 86 were identified as having DM and 112 were identified as pre-diabetic, accounting for 9.29% (95% CI: 7.11-11.47%) and 10.32% (95% CI: 8.11-12.52%), respectively. There were no DM cases among those with a viral load of 200 copies/ml and above.

Univariate analysis

Table 2 shows the results of the univariate analysis and the multivariate analysis of the factors associated with DM. Males had 3.2-fold higher odds of having DM than did females (OR = 3.27, 95% CI: 1.95-5.47). Those aged 40-49 had approximately 2-fold higher odds, and those aged 50-59 and those aged 60 and above had approximately 7-fold higher odds of having DM than did those below 40 years (OR = 2.27, 95% CI: 1.21-4.27; OR = 6.78, 95% CI: 3.36-13.71; OR = 6.95, 95% CI: 3.11-15.53, respectively). Those who were unemployed (OR = 2.67, 95% CI: 1.06-6.73 *vs.* government employees), current smokers (OR = 2.04, 95% CI: 1.33-3.13 *vs.* non-smokers), and those with BMI ≥ 25kg/m^2 (OR = 2.8, 95% CI: 1.69-4.62 *vs.* BMI < 25 kg/m^2) had higher odds of DM compared to the reference group. There were no significant associations between DM and monthly household income, exercise intensity level, current alcohol drinking, or fruit and vegetable intake.

Among the univariate analysis of HIV-related factors, years on ART and duration of ddI or d4T exposure were associated with DM. Those on ART for 11 years or more had 1.8 times higher odds of having DM compared to those on ART less than 11 years (OR = 1.84, 95% CI: 1.21-2.8). Those exposed to ddI or d4T for less than 3 years had 1.7 times higher odds of having DM (OR = 1.7, 95% CI: 1.04-2.75 *vs.* non-exposed). Those exposed more than 3 years also showed a non-significant trend toward higher odds of DM (OR = 1.53, 95% CI: 0.84-2.79 *vs.* non-exposed). In this study, the duration of LPV/r exposure was not associated with DM.

Table 1. Baseline Characteristics

Variables (n = 1,212)	n	%	Variables	n	%
Sex			Eat fruit every day		
Male	695	57.34	No	569	46.95
Female	517	42.66	Yes	591	48.76
Age			Missing	52	4.29
< 40	394	32.51	Eat vegetable every day		
40-49	612	50.50	No	212	17.49
50-59	133	10.97	Yes	934	77.06
≥ 60	73	6.02	Missing	66	5.45
Mean (SD)	43.80 (3.24)		Weight		
Injection drug use			Mean (SD)	57.56 (8.88)	
No	946	78.00	BMI ≥ 25 kg/m^2		
Yes	266	22.00	No	1,046	86.30
Occupation			Yes	140	11.55
Government employee	112	9.24	Missing	26	2.15
Non-government employee	118	9.74	Mean (SD)		
Farmer	239	20.00	Years since HIV diagnosis		
Self-employed	525	43.32	< 11 years	608	50.17
Student	10	0.83	≥ 11 years	604	49.83
Unemployed	187	15.43	Mean (SD)	11.64 (4.04)	
Missing	21	1.73	Years on ART		
Household monthly income			< 11 years	736	60.73
< 4,000,000 VND	317	25.74	≥ 11 years	476	39.27
4,000,000-7,999,999	515	42.49	Mean (SD)	10.25 (3.24)	
8,000,000 or more	261	21.53	Latest CD4 count		
Unknown	65	5.36	≥ 200	1,180	97.36
Missing	59	11.86	< 200	32	2.64
Exercise level (IPAQ)			Median (IQR)	527 (408-679)	
Low	389	32.10	Latest pVL		
Moderate	496	40.92	< 200 copies/mL	1,203	99.26
High	225	18.56	≥ 200 copies/mL	9	0.74
Missing	102	8.42	Duration of LPV/r exposure		
Smoking			No exposure	1,079	89.03
Not at all	793	65.43	< 7 years	33	2.72
Less than daily	115	9.49	≥ 7 years	100	8.25
Daily	237	19.55	Mean (SD)	8.27 (3.66)	
Missing	67	5.53	Duration of ddI/d4T exposure		
Alcohol current drinker			No exposure	810	66.83
No	629	51.90	< 3 years	250	20.63
Yes	528	43.56	≥ 3 years	152	12.54
Missing	55	4.54	Mean (SD)	2.87 (1.94)	

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPAQ, International Physical Activity Questionnaire; SD, standard deviation; VND, Vietnamese dong.

Multivariate analysis

In model 1, physical activity intensity was included despite non-significant associations in the univariate analysis. Male participants had twice the odds of DM compared to females (OR = 2.06, 95% CI: 1.13-3.76). Current smokers and BMI ≥ 25 kg/m^2 remained strongly associated with DM (OR = 1.68, 95% CI: 1.00-2.82; OR = 2.43, 95% CI: 1.44-4.13, respectively). Those aged 50 and above were also strongly associated with DM (aged 50-59, OR = 5.25, 95% CI: 2.52-10.91; aged 60 and above, OR = 5.21, 95% CI: 2.11-12.8). Unemployment status and physical activity intensity were not associated with DM.

In model 2, physical activity intensity, past exposure to LPV/r, ddI, and d4T were included despite non-significant associations in the univariate analysis. To avoid collinearity with years on ART, years since HIV diagnosis was excluded. After adjusting for the effect of HIV-related factors, the association between DM and males, those aged 50 and above, and those with BMI ≥ 25 kg/m^2 remained. Although there was no significance, we found borderline p-values in current smokers (OR = 1.67, 95% CI: 0.99-2.83, p = 0.057) and years on ART (OR = 1.65, 95% CI: 0.99-2.77, p = 0.056) in model 2. Those on ART for 11 years and above had approximately 1.6 times higher odds of DM than did those on ART for less than 11 years.

Discussion

The study examined the prevalence of DM among PLWH on ART at the national hospital in Hanoi, and the factors associated with DM. In the multivariate analysis, males, those aged above 50 years, and those with BMI ≥ 25 kg/m^2 were significantly associated with higher

Table 2. Factors associated with DM among PLWH

n = 1,212		Univariate analysis		Multivariate analysis			
				Model 1		Model 2	
Variable	Category	Odds ratio (95% CI)	*p**	Odds ratio (95% CI)	*p**	Odds ratio (95% CI)	*p**
Gender	Female	1.00		1.00		1.00	
	Male	3.27 (1.95-5.47)	< 0.001	2.06 (1.13-3.76)	0.019	2.04 (1.11-3.74)	0.022
Age group	< 40	1.00		1.00		1.00	
	40-49	2.27 (1.21-4.27)	0.011	1.76 (0.92-3.38)	0.087	1.5 (0.77-2.91)	0.23
	50-59	6.78 (3.36-13.71)	< 0.001	5.25 (2.52-10.92)	< 0.001	4.7 (2.25-9.84)	< 0.001
	≥ 60	6.95 (3.11-15.53)	< 0.001	5.21 (2.12-12.85)	< 0.001	4.66 (1.87-11.64)	0.001
Injection drug use	No	1.00					
	Yes	1.35 (0.84-2.16)	0.213				
Occupation	Government employee	1.00		1.00		1.00	
	Non-govt. employee	1.1 (0.36-3.38)	0.867	1.31 (0.41-4.23)	0.646	1.32 (0.4-4.31)	0.647
	Farmer	1.43 (0.55-3.72)	0.461	1.44 (0.54-3.89)	0.468	1.47 (0.54-3.98)	0.454
	Self-employed/student	1.44 (0.59-3.48)	0.421	1.37 (0.55-3.42)	0.496	1.4 (0.56-3.51)	0.478
	Unemployed	2.67 (1.06-6.74)	0.038	1.81 (0.69-4.75)	0.229	1.81 (0.69-4.77)	0.231
Household monthly income	< 4,000,000 VND	1.00					
	4,000,000-7,999,999	0.85 (0.51-1.41)	0.519				
	8,000,000 or more	0.86 (0.46-1.58)	0.617				
	Unknown	0.83 (0.31-2.27)	0.721				
Exercise level (IPAQ)	Low	1.00		1.00		1.00	
	Moderate	1.41 (0.86-2.31)	0.168	1.26 (0.74-2.12)	0.395	1.25 (0.74-2.13)	0.401
	High	1.1 (0.59-2.07)	0.761	1.02 (0.53-1.97)	0.959	0.97 (0.5-1.88)	0.927
Current smoker	No	1.00		1.00		1.00	
	Yes	2.04 (1.33-3.13)	0.001	1.67 (1-2.81)	0.051	1.67 (0.98-2.83)	0.059
Current alcohol drinker	No	1.00					
	Yes	1.2 (0.79-1.83)	0.396				
Eat fruit every day	No	1.00					
	Yes	1.08 (0.71-1.65)	0.707				
Eat vegetables every day	No	1.00					
	Yes	0.79 (0.46-1.37)	0.404				
BMI ≥ 25 kg/m^2	No	1.00		1.00		1.00	
	Yes	2.79 (1.69-4.62)	< 0.001	2.43 (1.43-4.13)	0.001	2.42 (1.42-4.12)	0.001
Years since HIV diagnosis	< 11 years	1.00					
	≥ 11 years	1.45 (0.95-2.21)	0.084				
Years on ART	< 11 years	1.00				1.00	
	≥ 11 years	1.84 (1.21-2.8)	0.004			1.66 (0.99-2.78)	0.056
Latest CD4 count	≥ 200	1.00					
	< 200	1.69 (0.58-4.92)	0.336				
Duration of LPVr exposure	No exposure	1.00				1.00	
	< 7 years	0.35 (0.05-2.61)	0.307			0.41 (0.05-3.22)	0.4
	≥ 7 years	0.85 (0.38-1.88)	0.685			0.63 (0.27-1.49)	0.292
Duration of ddI/d4T exposure	No exposure	1.00				1.00	
	< 3 years	1.70 (1.04-2.75)	0.033			1.37 (0.8-2.34)	0.249
	≥ 3 years	1.53 (0.84-2.79)	0.163			1.11 (0.55-2.26)	0.77

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPAQ, International Physical Activity Questionnaire; VND, Vietnamese dong. Model 1 includes traditional factors; model 2 includes traditional and HIV-related factors. *Wald test

odds of DM among PLWH. Current smoking and longer time on ART with marginal p-values were also possibly attributable to developing DM. There were no cases of active opportunistic infections or other complications that could increase insulin resistance and be included in the multivariate model. To the best of our knowledge, this is the first study that focuses on PLWH in Vietnam for DM prevalence.

The age-standardized prevalence of DM and pre-diabetes were 9.29% and 10.32% in the study participants, respectively. According to the STEPS survey Vietnam 2015, the prevalence of DM and pre-diabetes were 4.1% and 3.6%, respectively (*23*). Our results imply the possibility of higher DM prevalence among PLWH. One study reported premature age-related comorbidities such as CVD and DM among PLWH (*25*); the prevalence of concurrent presence of two or more NCDs in PLWH was similar to that of a cohort of the general population who were 10 years older. The higher DM prevalence in this study population could be explained by premature aging. This finding supports early DM screening for PLWH.

Our results showed that BMI ≥ 25kg/m^2 was an important risk factor for DM, consistent with other study findings (*13,26,27*). The impact of weight gain on the risk of DM has been reported to be greater among PLWH than that of people without HIV (*28*). Furthermore, several studies have reported that the use of an integrase strand transfer inhibitor such as dolutegravir

(DTG) is associated with increased weight gain (*29,30*). Because the Vietnamese ART guideline issued in 2019 recommended a DTG-containing regimen as first-line treatment (*31*), weight increase should be carefully managed to reduce the risk of DM.

A systematic review and meta-analysis reported that weight-reducing diets with or without exercise advice could reduce obesity in adults (*32*). To manage weight, healthy eating and exercise programs could be provided to PLWH. Although the association between vegetable intake and exercise intensity and DM was not statistically significant in this study, those factors might have been associated with weight gain. In general, vegetable consumption in Vietnam is high compared with that in other high-income countries (*33*). Also, a notable proportion of study participants engaged in farming, and approximately 60% of the participants reported moderate- to high-intensity exercise. However, there is a concern that rapid economic growth and urbanization may change dietary patterns and promote sedentary lifestyles (*6*). It is critical to preserve healthy dietary patterns and exercise habits among Vietnamese PLWH to maintain adequate weight and prevent DM.

Male sex was strongly associated with DM in this study, but the association between sex and DM has varied across different studies (*27,34*). Several studies have shown a higher risk of DM among female participants than among male participants (*27*). Also, it has been reported that female participants were more likely to gain weight following ART initiation (*35*), and therefore females may have higher risk of having DM. Although the result was not conclusive, both sexes should be similarly monitored with respect to weight gain.

Smoking has been identified as an important risk factor for DM, and it has been reported that prevalence of smoking was higher among PLWH than among the general population (*10,36*). In Vietnam, there is a large difference in smoking prevalence among men and women (45.3% among men and 1.1% among women in 2015). In addition, among males, the prevalence of current smoking was highest among those aged 45-64 years (55%), followed by those aged 25-44 years (53.3%), versus 24.3% in those aged 15-24 years (*37*). A smoking cessation program targeting older men living with HIV could be effective in preventing DM.

The results indicate possible associations of a longer period on ART with DM after adjustment for sociodemographic and traditional factors. Although it is generally considered that the traditional risk factors are primarily responsible for the higher risk of DM among PLWH (*2,38*), this result implies that HIV-related factors such as time on ART may be a contributor to hyperglycemia among PLWH in addition to traditional factors. Several studies have reported that the use of protease inhibitors such as LPV/r and nucleoside reverse transcriptase inhibitors such as ddI and d4T increased the risk of hyperglycemia or DM (*20-22*) although an association between duration of ddI, d4T and LPV/r exposure and DM was not found in our study. The association between longer ART period and DM might be partially explained by the effects of ddI, d4T and LPV/r on DM.

There were some limitations in the study. First, the study site was a large ART outpatient clinic at a specialized hospital, and most participants had been receiving ART at NHTD for several years, which may limit the generalizability of the study findings to other settings in Vietnam. Second, DM cases were identified based on plasma glucose. Unlike HbA1c, plasma glucose is prone to be affected by fasting status. The DM prevalence may have been overestimated if the fasting status of the participants were not fully ensured. Third, multiple factors are intricately associated with the pathogenesis of DM (*39*). The sample size of this study may not have been sufficient to detect a complex relationship between an array of factors; for example, only borderline p-values were found for the association between current smoking status and years on ART and DM. However, stronger associations may have been found if the sample size had been larger given the associations in univariate analysis. This study did not investigate the effect of Vietnamese-specific factors on DM, such as regional living habits. Future research could investigate the association.

Conclusion

In conclusion, the findings of this study imply that DM and pre-diabetes prevalence among PLWH are higher than among the general population. In the multivariate analysis, male sex, older age, and BMI $\geq$ 25 kg/m^2 were significantly associated with and current smokers and years on ART were possible risk factors for DM. Years on ART could be an important risk factor that will require clinical attention. Encouraging careful glucose monitoring in routine care and management of other risk factors would be beneficial to prevent developing DM among those on ART longer. Our findings suggest that interventions such as weight control and smoking cessation support could be provided at HIV outpatient clinics, contributing to DM prevention and early diagnosis. Integration of HIV/AIDS and NCDs services is essential to address health needs comprehensively and enhance health-related quality of life among PLWH.

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References

1. Patel P, Rose CE, Collins PY, Nuche-Berenguer B, Sahasrabuddhe VV, Peprah E, Vorkoper S, Pastakia SD, Rausch D, Levitt NS. NIH HIV/NCD Project Disease Condition Technical Operating Group. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: A systematic review and meta-analysis. AIDS. 2018; 32 Suppl 1:S5-S20.
2. Butt AA, McGinnis K, Rodriguez-Barradas MC, Crystal S, Simberkoff M, Goetz MB, Leaf D, Justice AC. Veterans Aging Cohort Study. HIV infection and the risk of diabetes mellitus. AIDS. 2009; 23:1227-1234.
3. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, Fraser S, Agan BK, Wegner S. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: A 20-year cohort study. AIDS. 2009; 23:41-50.
4. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, Grinspoon SK, Levin J, Longenecker CT, Post WS. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: A scientific statement from the American Heart Association. Circulation. 2019; 140:e98-e124.
5. International Diabetes Federation. IDF Diabetes Atlas 10th edition 2021. *https://diabetesatlas.org/data/en/country/217/vn.html* (accessd January 5, 2023).
6. World Health Organization. The growing burden of diabetes in Viet Nam. https://www.who.int/vietnam/news/feature-stories/detail/the-growing-burden-of-diabetes-in-viet-nam (accessed January 5, 2023).
7. Puhr R, Kumarasamy N, Ly PS, Ng OT, Van Nguyen K, Merati TP, Pham TT, Lee MP, Choi JY, Ross JL, Law MG. HIV and aging: Demographic change in the Asia-Pacific region. J Acquir Immune Defic Syndr. 2017; 74:e146-e148.
8. UNAIDS.VietNam. *https://www.unaids.org/en/regionscountries/countries/vietnam* (accessed Nov 19, 2021).
9. Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. Diabetes Care. 2015; 38:1804-1812.
10. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. JAMA. 2007; 298:2654-2664.
11. Giles ML, Gartner C, Boyd MA. Smoking and HIV: What are the risks and what harm reduction strategies do we have at our disposal? AIDS Res Ther. 2018; 15:26.
12. Petry NM. Alcohol use in HIV patients: What we don't know may hurt us. Int J STD AIDS. 1999; 10:561-570.
13. Han WM, Jiamsakul A, Kiertiburanakul S, *et al.* Diabetes mellitus burden among people living with HIV from the Asia-Pacific region. J Int AIDS Soc. 2019; 22:e25236.
14. Amberbir A, Banda V, Singano V, Matengeni A, Pfaff C, Ismail Z, Allain TJ, Chan AK, Sodhi SK, Van Oosterhout JJ. Effect of cardio-metabolic risk factors on all-cause mortality among HIV patients on antiretroviral therapy in Malawi: A prospective cohort study. PLoS One. 2019; 14:e0210629.
15. Hatleberg CI, Ryom L, d'Arminio Monforte A, Fontas E, Reiss P, Kirk O, El-Sadr W, Phillips A, de Wit S, Dabis F, Weber R, Law M, Lundgren JD, Sabin C. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. Association between exposure to antiretroviral drugs and the incidence of hypertension in HIV-positive persons: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. HIV Med. 2018; 19:605-618.
16. Prioreschi A, Munthali RJ, Soepnel L, Goldstein JA, Micklesfield LK, Aronoff DM, Norris SA. Incidence and prevalence of type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta-analysis. BMJ Open. 2017; 7:e013953.
17. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. *https://apps.who.int/iris/bitstream/handle/10665/43588/9241594934_eng.pdf?sequence=1&isAllowed=y* (accessed January 5, 2023).
18. Sjostrom M, Ainsworth B, Bauman A, Bull F, Hamilton-Craig C, Sallis J. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)—Short and Long Forms. *https://www.researchgate.net/file.PostFileLoader.html?id=5641f4c36143250eac8b45b7&assetKey=AS%3A294237418606593%401447163075131* (accessed January 5, 2023).
19. World Health Organization. STEPwise approach to noncommunicable disease risk factor surveillance (STEPS). *https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps* (accessed January 5, 2023).
20. Noor MA, Flint OP, Maa JF, Parker RA. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: Demonstrable differences *in vitro* and clinically. AIDS. 2006; 20:1813-1821.
21. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte ADA, Fontas E, Law MG, Friis-Møller N, Phillips A. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Incidence and risk factors for new-onset diabetes in HIV-infected patients: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. Diabetes care. 2008; 31:1224-1229.
22. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: A 5-year cohort study. Arch Intern Med. 2000; 160:2050-2056.
23. Phu TD, Bac TD, Bao TQ, Toan HH. National Survey on the Risk Factors of Non-Communicable Diseases (Steps) Viet Nam 2015. Hanoi, Vientam, 2016; pp.11.
24. Matsumoto S, Nagai M, Luong DAD, Nguyen HDT,

Nguyen DT, Dinh TV, Tran GV, Tanuma J, Pham TN, Oka S. Evaluation of SARS-CoV-2 antibodies and the impact of COVID-19 on the HIV care continuum, economic security, risky health behaviors, and mental health among HIV-infected individuals in Vietnam. AIDS Behav. 2022; 26:1095-1109.
25. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011; 53:1120-1126.
26. da Cunha GH, Franco KB, Galvão MTG, Lima MAC, Fontenele MSM, Siqueira LR, Ramalho AKL, Fechine FV. Diabetes mellitus in people living with HIV/AIDS: Prevalence and associated risk factors. AIDS Care. 2020; 32:600-607.
27. Nguyen CT, Pham NM, Lee AH, Binns CW. Prevalence of and risk factors for type 2 diabetes mellitus in Vietnam: A systematic review. Asia Pac J Public Health. 2015; 27:588-600.
28. Herrin M, Tate JP, Akgün KM, Butt AA, Crothers K, Freiberg MS, Gibert CL, Leaf DA, Justice AC, Rimland D, Rodriguez-Barradas MC, Ruser CB, Herold KC. Weight gain and incident diabetes among HIV infected-veterans initiating antiretroviral therapy compared to uninfected individuals HHS public access. J Acquir Immune Defic Syndr. 2016; 73:228-236.
29. Norwood J, Turner M, Bofill C, Rebeiro P, Shepherd B, Bebawy S, Hulgan T, Raffanti S, Haas DW, Sterling TR, Koethe JR. Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr. 2017; 76:527-531.
30. Rebeiro PF, Jenkins CA, Bian A, *et al.* Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor-based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. Clin Infect Dis. 2020; 73:e2234-2242.
31. Bo Y tế. HƯỚNG DẪN ĐIỀU TRỊ VÀ CHĂM SÓC HIV/AIDS. Hanoi, Vietnam, 2019; pp. 144. (in Vietnamese).
32. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ. 2017; 359:j4849.
33. Harris J, Nguyen PH, Tran LM, Huynh PN. Nutrition transition in Vietnam: changing food supply, food prices, household expenditure, diet and nutrition outcomes. Food Sec. 2020; 12:1141-1155.
34. Pham NM, Eggleston K. Prevalence and determinants of diabetes and prediabetes among Vietnamese adults. Diabetes Res Clin. 2016; 113:116-124.
35. Sax PE, Erlandson KM, Lake JE, *et al.* Weight gain following initiation of antiretroviral therapy: Risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020; 71:1379-1389.
36. Jaquet A, Dabis F. Smoking status and HIV in low-income and middle-income countries. Lancet Glob Health. 2017; 5:e557-e558.
37. Van Minh H, Giang KB, Ngoc NB, Hai PT, Huyen DTT, Khue LN, Lam NT, Nga PTQ, Quan NT, Xuyen NT. Prevalence of tobacco smoking in Vietnam: Findings from the Global Adult Tobacco Survey 2015. Int J Public Health. 2017; 62(Suppl 1):121-129.
38. Althoff KN, Gebo KA, Moore RD, *et al.* Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: A collaboration of cohort studies. Lancet HIV. 2019; 6:e93-e104.
39. Kyrou I, Tsigos C, Mavrogianni C, *et al.* Sociodemographic and lifestyle-related risk factors for identifying vulnerable groups for type 2 diabetes: A narrative review with emphasis on data from Europe. BMC Endocr Disord. 2020; 20 (Suppl 1):134.

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Does increasing the number of beds or health workers contribute to the rational use of scarce public health resources?

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Abstract: Turkey makes substantial investments to increase the number of qualified beds in hospitals, the shortage in health professionals remains one of the main obstacles of the health system in the country. To address this research gap, the study aims to formulate a rational solution for the dilemma on whether to invest in beds or health professionals contribute to the rational use of scarce public health resources. Data for testing the model were derived from the Turkish Statistical Institute across 81 provinces in Turkey. The path analytic approach was used to determine the associations among hospital size, utilization/facility, health workforce, and indicators of health outcomes. The results point to a strong link between quantity of qualified beds, utilization of health services, and facility indicators, and health workforce. Rational use of scarce resources, optimal capacity planning, and increased quantity of health professionals will be beneficial for the sustainability of health care services.

***Keywords*:** hospital size, utilization, facility, health workforce, health outcomes, Turkey

Introduction

Resource planning for nonprofit health care organizations is critical (*1*) for better management of limited public health resources. Enhanced coordination among departments is key to each stage of planning, response, and recovery of health care services (*2*) as the global public health crisis continues to be a threat to health and economy (*3*). Moreover, pressures from cost containment and the Covid-19 pandemic force health care institutions to re-examine decisions regarding human resource management and facilities and their utilization (*4*). Previous studies argued that effective coordination among health care services is critical during health crises (*3*). Specifically, research on facility management decisions in health care indicate that decisions on facility acquisition and utilization may influence the management of workforce and equipment and the performance of hospitals in terms of cost and quality (*5,6*). Large-scale hospital construction and operation in countries with mixed economies feature public–private partnerships (*7*). The previous literature mentions that decisions regarding facility management are long term. Thus, measuring their impact on health care operations in the short run is impossible (*8*).

In Turkey, the Ministry of Health (MoH) made substantial investments in city hospitals under the Health Transformation Program (*9*). The reason behind these capacity enhancement decisions is to respond to increase in demand for health services and to improve the quality of such services (*10*). The distinguishing feature of city hospitals was that they are physically large and built within large complexes since 2017. To this day, many of these hospitals remain under construction. Moreover, investment in 10 city hospitals enabled the establishment of health services in campuses across cities as of 2020 (*9*). However, the Covid-19 pandemic increased the need for the better planning of health services and critical care to respond to the need for rapid, innovative, and cost-effective response to unforeseen health crises (*11*). The presence of gaps in critical care capacity and scarcity of health professionals became obvious in the majority of countries worldwide after the outbreak of the Covid-19 pandemic (*12,13*). Indeed, a common lore of capacity management stated that strategies for capacity improvement should be pursued based on the various sizes and locations of facilities. Moreover, as their size increases, hospitals should place increased emphasis on decisions regarding facility management (*8,14*). In this regard, effective capacity planning can significantly enhance the capability and effectiveness of treatment for critical care patients due to a tremendous health crisis (*15*).

Demographics and the variety of services of hospitals are frequently used to categorize hospitals and are used as a criterion for comparing decisions on capacity management (*16*). A common factor for determining hospital size is the number of beds, wherein large-scale hospitals tend to contain more capacity for idle facilities than small-scale hospitals. This scenario is a result of the

nationwide decrease in hospital occupancy ratios (*8*). In this regard, if large-scale hospitals fail to appropriately manage facility utilization, then they may jeopardize cost and quality performance relative to competitors (*17*). In other words, facility management is considered the front end in a hospital resource planning system, which describes the capacity resource required to perform the various activities according to priority (*5*). Facility management decisions typically examine issues related to hospital inpatient admission and average length of stay. In addition, bed occupancy rate provides an overview of the level of utilization of beds in the hospital (*18*). The higher the bed occupancy rate, the lower the capacity to admit new patients (*19*).

Conversely, the literature suggests a causal inter-relationship between facility, utilization, and workforce management of health services (*20*). Growth in the number of individuals living with chronic conditions is a major driver of health care costs, whereas the utilization of primary care provider, nurse, and physician services is associated with less use of acute care services and less total costs (*21*). Facility management throughout outpatient capacity expansion and demand management are helpful measures for meeting time-varying demands and for improving utilization (*8*). Health professionals are pressured to deliver effective, efficient services by considering the skill mix of the workforce, particularly the staffing of new services (*22*). Health care organizations are established in response to demand (*23*). Thus, considering the appropriate number of health professionals is useful for guiding service planning and delivery, where the supply of health professionals exerts a powerful force in changing the health care system (*23,24*). However, the Covid-19 pandemic has led to drastic changes in bed capacity and physician and nursing workforce requirements (*25*), such that the availability of number of beds, critical care capacity, and health workforce supply during health crises have become current topics of interest to researchers on health care capacity planning (*26*). In-depth understanding of hospital capacity, workforce, and outcome inter-relationships have strongly advocated for the preparedness of health systems in terms of effective management of crisis situations (*27*). As such, better management of health care capacity and preparedness for times of crisis is critical for developing countries (*28*). In Turkey, investments in city hospitals include a large quantity of qualified beds to provide relief to health policy makers during the pandemic with regard to providing better responses to the sudden increase in demand for health services (*29*). Moreover, despite the fact that Turkey lags behind developing countries in terms of number of physicians and nurses (*30*), the sacrifice and outstanding performance of Turkish physicians and nurses proved essential to the country's fight against the pandemic (*31*). Existing knowledge emphasizes that increase in hospital size and human resources have a direct impact on health services utilization such as average length of stay and bed occupancy rate (*32*) and this will lead to an increase in number of health professionals. Because limited numbers of physicians and nurses, in addition to high bed occupancy rate may be significant drivers of mortality (*33*). Increase in health services utilization and health workforce results in an increase in health outcomes such as death rates (*34*). However, high burden of health services utilization and increase in health facilities is interrelated with amount of human health resources. High number of health professionals is necessary to answer an increase in health services utilization and facilities. Negative causal transmission between health services utilization and facility indicators and health workforce can be a result under the mediating effect of an increase in burden of health services. In this vein, a lack of a number of health professionals are not responding to that increase. This necessitates a better understanding and better planning of health services performance indicators in developing countries. Thus, the rationalization of decisions regarding new health care facility investment and rational capacity planning is critical for enhancing the management of scarce health resources and improving health outcomes in Turkey. Bearing this in mind, the purpose of this experiment sought to understand the nexus between hospital size, health services utilization and facility management, health workforce and health outcomes. The following sections present the conceptual study model and hypotheses, the study results, and a discussion of the key study findings.

Methods

Conceptual model and hypothesis

Figure 1 presents the conceptual model of the relationship between hospital size, utilization and facility of health services, health workforce and health outcomes. The theoretical basis of this model is based on interrelationships between intermediate operations decisions and health outcomes (*35*). The study model and conceptual framework of this study inspired from the literature (*36*) has been built by the author and the hypotheses developed based on comprehensive literature review by focusing on these factors relationship. The following part of the study reviews literature and develops hypotheses that link selected variables, which include the number of hospitals and qualified beds, utilization and facility indicators of health services, number of health workforce and health outcomes.

Hospital size

The hospital size factor is assessed by the number of beds. Generally, large hospitals tend to have more idle capacity than smaller hospitals and increase in number of

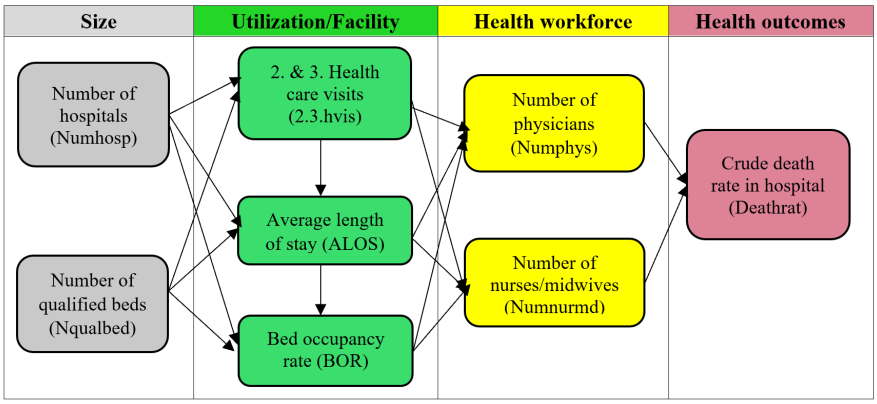


Figure 1. Conceptual model. *Adapted from reference (*36*).

hospitals and beds will lead to an increase in utilization and facility indicators of health services (*8,14,37*).

The related hypotheses are as follows:

H1a: The increase in number of hospitals will lead to an increase in secondary and tertiary health care visits.

H1b: The increase in number of hospitals will lead to an increase in average length of stay.

H1c: The increase in number of hospitals will lead to an increase in bed occupancy rate.

H1d: The increase in number of qualified beds will lead to an increase in secondary and tertiary health care visits.

H1e: The increase in number of qualified beds will lead to an increase in average length of stay.

H1f: The increase in number of qualified beds will lead to an increase in bed occupancy rate.

Utilization and facility indicators of health services

Improving the administrative planning of utilization and facility of health services is critical for the management of scarce health resources. The literature stated that an increase in health care visits is strongly associated with average length of stay because it indicates increased bed occupancy rate (*38,39*).

The related hypotheses are as follows:

H2a: The increase in secondary and tertiary health care visits will lead to an increase in average length of stay.

H2b: The increase in average length of stay will lead to an increase in bed occupancy rate.

Health workforce

The literature has long discussed the inter-relationships between the increase in hospital utilization and supply of health professionals (*40,41*). Many studies have stated that developing countries should improve data on their workforce and changing population needs. Moreover, they should integrate new professional roles into their workforce planning models to better respond to health needs during crises (*42*).

H3a: The increase in secondary and tertiary health care visits will lead to an increase in number of physicians.

H3b: The increase in secondary and tertiary health care services will lead to an increase in number of nurses and midwives.

H3c: The increase in average length of stay will lead to an increase in number of physicians.

H3d: The increase in average length of stay will lead to an increase in number of nurses and midwives.

H3e: The increase in bed occupancy rate will lead to an increase in number of physicians.

H3f: The increase in bed occupancy rate will lead to an increase in number of nurses and midwives.

Health outcomes

Standardized mortality rates, infant mortality, life expectancy and potential lost years of life have traditionally been used as health outcome indicators (*43*). The number of physicians (supply) is associated with population mortality (*44,45*). Moreover, not only physician but also nurse staffing characteristics can lead to the formulation of strategies that aim to reduce mortality and prevent unnecessary deaths (*46*). Increasing health care service utilization and improving health care facilities necessitates an increase in the number of health professionals, such as physicians and nurses/midwives. Indicators of health care utilization and facility and workforce availability are closely related to health outcomes, such as number of deaths.

The related hypotheses are as follows:

H4a: The increase in number of physicians will lead to an increase in crude death rate in hospital.

H4b: The increase in number of nurses and midwives will lead to an increase in crude death rate in hospital.

Data

In this study, data gathered from official Turkish

Ministry of Health-Health Statistics Yearbook-2018 legal online records (*https://dosyasb.saglik.gov.tr/Eklenti/36164,siy2018en2pdf.pdf?0*). Study variables presents data for 81 provinces of Turkey for the year 2020 (*30*). There is no need for ethical approval for this study. Detailed explanations about study variable descriptions, labels, years and data sources are represented in Table 1.

Results

Descriptive statistics

Table 2 presents descriptive statistics of study variables. Median, minimum, maximum, and standard deviation values are represented. Because of non normal distribution of study variables, median values are also presented. The mean value of number of hospitals in 81 provinces is 18.94 (± 27.82), number of qualified beds is 1,721.02 (± 2,740.27), number of secondary and tertiary health care visits is 6,382,950 (± 11,589,451.42), bed occupancy rate is 65.92 (± 7.62), average length of stay is 4.05 (± 0.69), number of physicians is 1,883 (± 4,202), number of nurses and midwives is 3,051 (± 5,079), crude death rate in hospital is 16.16 (± 5.79).

Path analytic models

Before constructing the path analytic models, Spearman rank correlations between study variables indicated that there is no fear for multicollinearity in this study. First path analytic model results performed on the variance-covariance matrix is presented in Figure 2. The whole model is significant ($p < 0.001$); however certain path links of the model include insignificant "t" values (Figure 2). The "t" values, presented in "red" color for the number of hospitals [Numhosp] and average length of stay [ALOS]; average length of stay [ALOS] and bed occupancy rate [BOR]; bed occupancy rate [BOR] and number of nurses/midwives [Numnurmd]; number of physicians [Numphys] and crude death rate in hospital [Deathrat], are insignificant ($p > 0.05$). Due to non meaningful "t" values in the first path model, the path links from Numhosp to ALOS, ALOS to BOR; BOR to

Table 1. Variable descriptions and labels

Variable group	Variables	Explanations	Year	Labels
Size	Number of hospitals	Total number of MoH, university, private and other hospitals.	2018	Numhosp
	Number of qualified beds	Qualified bed is a bed with a bathroom, a toilet, and a maximum of 2 patient beds, television, telephone, refrigerator, dining table, shelf and a folding companion seat. These figures are included in the total number of beds.	2018	Nqualbed
Utilization	Secondary and tertiary health care visits	Total number of secondary and tertiary health care visits by province.	2018	2.3.hvis
Utilization	Bed occupancy rate	This indicates the rate of bed usage by the patient within one year. It is calculated as follows: (Number of Days Stayed × 100) / (Number of Beds × 365).	2018	BOR
Facility	Average length of stay	The average number of days a patient stays in a hospital. It is calculated as follows: (Number of Days Stayed) / (Discharged + Deceased).	2018	ALOS
Health workforce	Number of physicians	Total number of specialist physicians, general practitioners and medical residents.	2018	Numphys
	Number of nurses/midwives	Total number of nurses and midwives.	2018	Numnurmd
Health outcomes	Crude death rate in hospitals (‰)	It indicates the proportion of patients who died in a hospital within a year to those who died and discharged from the hospital in the same period. (Deceased × 1.000) / (Discharged + Deceased)	2018	Deathrat

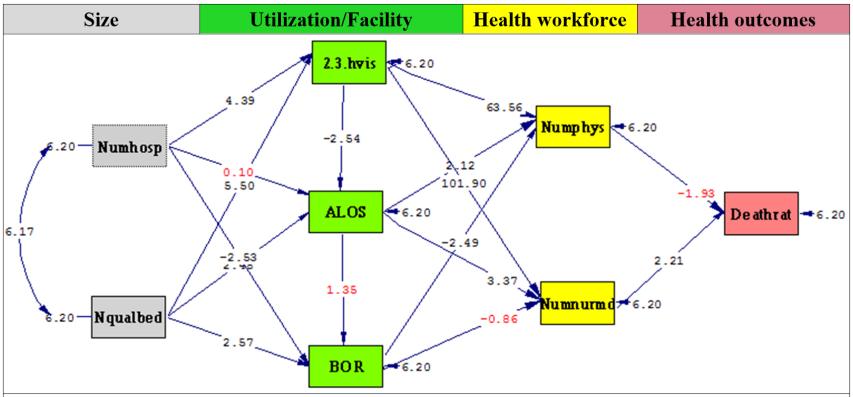
Table 2. Descriptive statistics

Variable group	Variables	N	Min	Max	Median	Mean	SD
Size	Number of hospitals	81	1	236	12	18.94	27.82
	Number of qualified beds	81	108	22278	999	1721.02	2740.27
Utilization	Secondary and tertiary health care visits	81	409,722	94,393,122	3,247,625	6,382,950	11,589,451.42
Utilization	Bed occupancy rate	81	46.9	84.7	66.30	65.92	7.62
Facility	Average length of stay		2.6	6.1	4	4.05	0.69
Health workforce	Number of physicians	81	112	33052	740	1883	4202
	Number of nurses/midwives	81	281	40618	1763	3051	5079
Health outcomes	Crude death rate in hospitals	81	2.8	29.3	16.60	16.16	5.79

Numnurmd, Numphys to Deathrat were excluded from the first path analytic model. Therefore, H1b, H2b, H3f and H4a were rejected. After the exclusion of the non meaningful path links of the prior model, a redefined second path analytic model was constructed and presented in Figure 3.

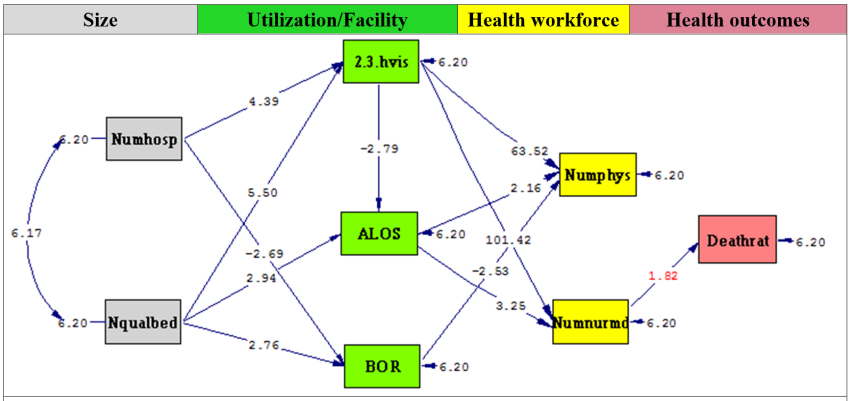
Second path analytic model results performed on the variance-covariance matrix is presented in Figure 3. The whole model is significant ($p < 0.001$); however, one of the path links of the model include insignificant "t" values (Figure 3). The "t" value, presented in "red" color for the number of nurses/midwives [Numnurmd] and crude death rate in hospital [Deathrat] is insignificant ($p > 0.05$). Because of non meaningful "t" value of the second path model, the path link from [Numnurmd] to [Deathrat] was excluded from the model and H4b was rejected. After the exclusion of the insignificant path link from the model, "t" values and standard path coefficients obtained from a redefined final path model was constructed and presented in Figure 4 and Figure 5, respectively.

Figure 4 represents final path analytic model. This model presents a causal interrelationship between hospital size, utilization and facility of health care services and health workforce indicators. We hypothesized that the increase in number of hospitals will lead to an increase in secondary and tertiary health care visits. As expected, the increase in number of hospitals led to an increase in secondary and tertiary health care visits (PC = 0.44; t = 4.39; $p < 0.01$). Therefore, H1a was accepted. Additionally, we hypothesized that the increase in number of hospitals will lead to an increase in bed occupancy rate. Interestingly, study findings show that the increase in number of hospital has a strong negative effect on an increase in bed occupancy rate (PC = -2.04; t = -2.69; $p < 0.01$). Therefore, H1c was rejected. Moreover, we hypothesized that an increase in number of qualified beds will lead to an increase in secondary and tertiary health care visits. As expected, the increase in number of qualified beds will lead to an increase in secondary and tertiary health care visits (PC = 0.55; t = 5.50; $p < 0.01$). Thus, H1d was accepted. Furthermore,



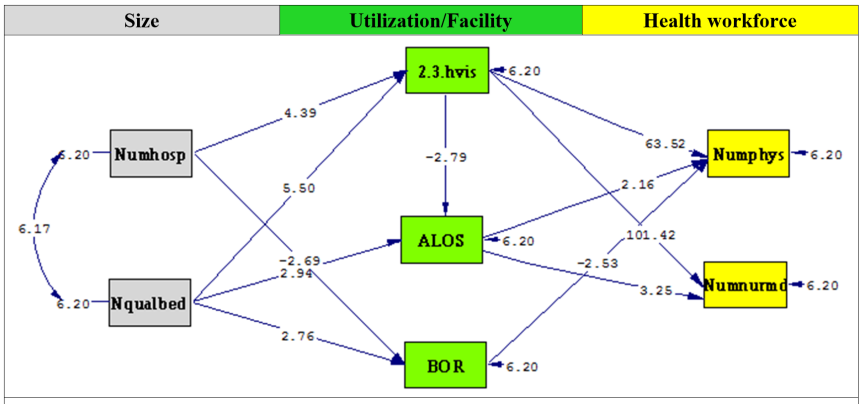
Path analytic model (t values). See Table 1 for description of variables. See Table 3 for global fit indices obtained from first model. Numbers associated with single headed arrows are t-values. t-values which are greater than 1.96 and 2.56 are meaningful at 0.05 and 0.01 levels, respectively.

Figure 2. First path analytic model (t values).



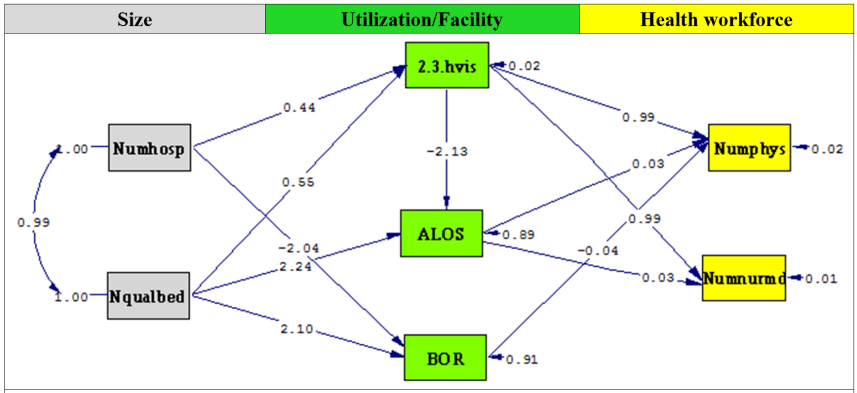
Path analytic model (t values). See Table 1 for description of variables. See Table 3 for global fit indices obtained from second model. Numbers associated with single headed arrows are t-values. t-values which are greater than 1.96 and 2.56 are meaningful at 0.05 and 0.01 levels, respectively.

Figure 3. Second path analytic model (t values).



Path analytic model (t values). See Table 1 for description of variables. See Table 3 for global fit indices obtained from second model. Numbers associated with single headed arrows are t-values. t-values which are greater than 1.96 and 2.56 are meaningful at 0.05 and 0.01 levels, respectively.

Figure 4. Final path analytic model (t values).



Numbers associated with single headed arrows are standardized path coefficients. Standart path coefficients indicate significant relations of final model. The coefficients with absolute values less than 0.01 may indicate "small" effect, values around 0.30 "medium" effect, values greater than 0.50, a "large" effect.

Figure 5. Final path analytic model (standard path coefficients).

we hypothesized that the increase in number of qualified beds will lead to an increase in average length of stay. As expected, the increase in number of qualified beds will lead to a strong increase in average length of stay (PC = 2.24; t = 2.94; $p < 0.01$). Therefore, H1e was accepted. Additionally, we hypothesized that an increase in number of qualified beds will lead to an increase in bed occupancy rate. As expected, the increase in number of qualified beds led to an increase in bed occupancy rate (PC = 2.10; t = 2.76; $p < 0.01$). Thus, H1f was accepted. Moreover, we hypothesized that, an increase in secondary and tertiary health care visits will lead to an increase in average length of stay. However, it is seen that an increase in secondary and tertiary health care visits have a negative effect on an increase in average length of stay (PC = -2.13; t = -2.79; $p < 0.01$). Therefore, H2a was rejected. On the other hand, a causal relationship between health care utilization and facility indicators and health workforce was characterized by the relation between secondary and tertiary health care visits and number of physicians. We hypothesized that the increase in secondary and tertiary health care visits will lead to an increase in number of physicians. As expected, the increase in number of secondary and tertiary health care visits has a very strong effect on an increase in number of physicians (PC = 0.99; t = 63.52; $p < 0.01$). Thus, H3a was accepted. Moreover, we hypothesized that the increase in secondary and tertiary health care visits will lead to an increase in number of nurses/midwives. As expected, the increase in number of secondary and tertiary visits has a very strong effect on an increase in number of nurses/midwives (PC = 0.99; t = 101.42; $p < 0.01$). Therefore, H3b was accepted. Furthermore, we hypothesized that, an increase in average length of stay will lead to an increase in number of physicians. It is seen that, the increase in average length of stay will lead to a small increase in number of physicians (PC = 0.03; t = 2.16; $p < 0.05$). Thus, H3c was accepted. Moreover, we hypothesized that, the increase in average length of stay will lead to an increase in number of nurses and midwives. As expected, the increase in average length of stay has a small positive effect on an increase in number

Table 3. Global fit indices obtained from first, second and final path models

Index	First model	Second model	Final model
Chi-square (X^2)	72.03	77.98	53.60
Df	11	15	9
p	< 0.001	< 0.001	< 0.001
NFI	0.87	0.86	0.89
CFI	0.87	0.87	0.90
GFI	0.81	0.80	0.84
RMSEA	0.268	0.234	0.254

Abbreviations: Df: Degrees of freedom; NFI: Normed fit index; CFI: Comparative fit index; GFI: Goodness of fit index; RMSEA: Root mean square error of approximation.

of nurses and midwives (PC = 0.03; t = 3.25; $p < 0.01$). Therefore, H3d was accepted. Finally, we hypothesized that an increase in bed occupancy rate will lead to an increase in number of physicians. Interestingly, study findings emphasize that, an increase in bed occupancy rate has a small negative effect on an increase in number of physicians (PC = -0.04; t = -2.53; $p < 0.05$). Therefore, H3e was rejected.

Table 3 represents global fit indices the ratios derived by dividing Chi-square (X^2) by degree of freedom (Df) (X^2/Df) were also examined. Note that, X^2/Df ratio less than 2 was considered a "perfect" model fit, whereas one that is less than 3 was considered as a "medium" model fit, and one less than 5 was considered as a "small" indicator of model fit (*47*). According to the X^2/Df (53.60/9=5.9) value obtained from the final model, it is clear to say that final path model indicates an acceptable model fit. Moreover, we used multiple criteria of model fit indices besides X^2 statistics, because X^2 statistics are influenced by sample size and number of variables in the dataset (*48*). Other fit indices obtained from the final path model include the normed fit index (NFI), comparative fit index (CFI) and goodness of fit index (GFI). The NFI is 0.89, CFI is 0.90 and GFI is 0.84, indicating acceptable model fit (*43,44*) between final model and the dataset, as seen in Table 3.

Discussion

Key findings

The study aimed to answer the research question: "*Is investment in the number of beds or health professionals a priority for the rational use of scarce health resources in Turkey?*" The key findings indicate that, an increase in the number of qualified beds exerted a strong positive effect on the increase in facilities and indicators of the utilization of health services. However, an increase in average length of stay indicates an extremely small positive effect on increases in the number of physicians and nurses/midwives. Moreover, an increase in bed occupancy rate led a decrease in the number of physicians moderated by the direct positive effect of the increase in the number of qualified beds. The findings highlight that an increase in the number of qualified beds exerts a direct and strong positive effect on the increase in utilization and health services facility indicators. However, an increase in average length of stay and bed occupancy rate did not exhibit a strong positive effect on the increase in the number of physicians and nurses/midwives. Moreover, the increase in the number of hospitals displays a medium positive effect on the increase in secondary and tertiary health care visits, which leads to a strong positive effect on the increases in the number of physicians and of nurses/midwives.

A surprising finding of this research, which is related to the research question, is that an increase in the number of hospital beds exerts a strong negative effect on the increase in bed occupancy rate. In relation to this finding, the increase in bed occupancy rate displays a slight mediating negative effect on the increase in the number of physicians. In other words, an increase in the number of qualified beds clearly displays a strong positive effect on the increase in utilization and facility indicators of health care services. However, the increase in utilization and facility indicators of health services exhibits a negative and a slight positive effect on increases in the number of physicians and nurses/midwives. The findings suggest that public health policy makers should prioritize the number of health professionals to maximize the scarce health resources in Turkey. By focusing on the inter-relationships between the size of health services, utilization, facility and health workforce indicators, the broad scope of the study will appeal to all scholars interested in the field of health care capacity and health workforce indicators.

Moreover, the findings elucidate the strong negative inter-relationships between the utilization of health services and indicators of the health workforce. A clear concept identified is that a positive relationship between an increase in the utilization of health services on the increase in the indicators of the health workforce is desirable. However, the findings are unique and emphasize that an increase in bed occupancy rate leads to a decrease in the number of physicians. The results of this study are in line with current health statistics of Turkey. The scarcity of number of health workforce such as physicians is noticeable in Turkey. In terms of total number of physicians per 100,000 population, Turkey lags behind all developed Organization for Economic Co-operation and Development (OECD) countries with 205 doctors in 2019, compared to 356 in the OECD average. The acute bed occupancy rate in Turkey was 65.3% in 2009 and 65.5% in 2019, while the OECD average was 76% for 2019 (*49*). The results of this study shows that the increase in bed occupancy results in a decrease in number of physicians. This result highlights that, human resources are failing to respond the growing needs of health facilities such as increase in the number of beds. This finding critically emphasizes the necessity

of reinforcing the number of health professionals to enable better responses to global health challenges. In other words, the rational use of scarce resources and better planning of health human resources are urgent to better cater to the need for high-capacity health care services apart from building new hospitals and expanding the current capacity of such services as the primary motivations of the Health Transformation Program in Turkey. However, the lack of health professionals in Turkey is notable compared with that of developed countries (*49*). Additionally, the Covid-19 pandemic increased the urgency for the development of the health workforce (*35*). Thus, increasing the number of health professionals is key to future sustainability and better preparedness during health crises (*12*). The findings pose several important implications for future studies by emphasizing the strong inter-relationships between health care capacity, utilization, and indicators of facility and health workforce. Notably, the findings do not support the inter-relationships between size, utilization/facility, health workforce indicators, and health outcomes. In light of these study findings, future researchers will benefit from further investigation for a better understanding of the inter-relationships between health care capacity, health workforce, and health outcome. The findings bolster the claim that an increase in investment for qualified beds increases the utilization of health services and facility indicators. However, increases in average length of stay and bed occupancy rate did not exhibit a strong positive effect on the increase in the number of physicians, nurses, and midwives. A common view in public health care capacity planning suggests that the degree of increase in the utilization of health services leads to an increase in the number of health professionals (*42*). The current results differ from this view and demonstrates that an increase in bed occupancy rate exerts a negative effect on the number of physicians. At the heart of this finding lies the objective to highlight the need for improvement in health human resource planning in Turkey.

The key findings reveal that increasing the number of hospitals and qualified beds can lead to an increase in the utilization and facility indicators of public health care services. However, an increase in utilization and facility indicators of health care services does not lead to an increase in the number of the health workforce, such as physicians, nurses, and midwives. Moreover, the increase in health workforce does not exert a strong positive effect on health outcome even with the mediating effect of the increase in utilization and facility indicators of health services. In summary, the findings highlight the positive inter-relationship between hospital size/utilization of health services and facility indicators but not between utilization and facility indicators of health services with health workforce with the indirect effect of the increase in hospital size. The results can help broaden the vision of public health policy makers in their decisions regarding capacity enhancement, public resource management and recommend a balanced capacity management approach that aims not only to invest for the improvement of hospital size but also for the increase in the number of health professionals.

Strengths of this study

The study makes several contributions that can enhance the understanding of the inter-relationship between hospital size, utilization and facility indicators of health services, and number of health professionals. This empirical study allows us to examine a novel way the interrelationship between public health facilities and health human resources. Study findings bring many lights for rational distribution and better management of public health resources. In Turkey, substantial investments in city hospitals is common, which leads to high capacities for qualified beds (*10*). However, operational planning of health services is crucial and should thus be improved for the rational management of scarce health resources. To the best of our knowledge, a paucity in the research on the adequacy of health professionals in Turkish health care continues. Thus, the results of the present study aims to fill this research gap by emphasizing the strong associations between hospital size, utilization, and facility indicators of health services, and workforce indicators. The findings can serve as reference for certain general decisions for the support of health care professionals operating in a fast-moving health care environment. An added strength of this study lies in its emphasis of enhancing the understanding on the negative effect of increased bed occupancy rate on increased number of physicians. This finding strongly emphasizes the need for better health human resource management and increased number of health professionals in Turkey. As such, the current deficit in the number of health professionals that persists in developed countries is critical to the response to international health crises (*3*). Health policy makers and planners can use the findings to increase awareness of the need to reinforce the current workforce and to consider equity during the geographic distribution of the health workforce.

Limitations and recommendations for future studies and public health policy makers

The study has limitations that are worth noting. First, the findings are based on a secondary dataset derived from the Turkish Ministry of Health Statistical Yearbook for 2018 (*30*). In this regard, the researchers acknowledge the limited control over the type of data available. Thus, the study strongly suggests that future studies should include primary datasets in the analysis based on the operational efficiency and performance indicators of public city hospitals. In addition, the findings emphasize the strong negative effect of increased bed occupancy

rate on increased number of physicians. In Turkey, health policy makers should initially mainly focus on the development of health workforce supply. In light of these results, future studies are required to provide in-depth understanding of the adequacy and responsiveness of health human resources in terms of efforts to improve health care capacity. Furthermore, health policy makers in Turkey should prioritize issues related to capacity filling and effective planning of health human resources. Ensuring more involvement from key stakeholders of the health system in the facility and utilization decisions of the health system is crucial. In addition, the voices of the public and health professionals should be heard during the formulation of capacity enhancement decisions. Health planners should ensure more transparency during the bid–offer process for public–private partnerships during the hospital-building stages. Health planners and policy makers should provide a rational basis for the question "Can one-size hospitals respond to the need of the Turkish population after considering accessibility to health services and rural–urban discrepancies?"

Conclusions

The results demonstrate strong inter-relationships between hospital size, utilization of health services and facility indicators of the health workforce. The findings should be considered during the operational planning of health services and integrated into health human resource planning and development. Additionally, the results are expected to appeal to many public health policy makers who are interested in effective health workforce planning. Additional research and better planning of the number of health human resources are required for the strategic development of health care operations and services. In summary, the results elucidate that increased bed occupancy rate exerts a negative effect on increased number of physicians in Turkey despite the fact that one of the motivations for building new hospitals is to improve bed capacity. In other words, capacity filling problems exist in the health system in Turkey. Thus, effective health human resource planning and rational demand forecasting should be essential components of public health policy making to better respond to the increasing demand for and utilization of health services.

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References

1. AbouAssi K, Jo S, Bies A. Human resources in nonprofits: An indicator of managerial preparedness or program needs? Public Performance & Management Review. 2022; 45:557-581.
2. Saltman DC. Is COVID-19 an opportunity to improve virtual leadership? Aust J Gen Pract. 2020; 49.
3. Nicola M, Sohrabi C, Mathew G, Kerwan A, Al-Jabir A, Griffin M, Agha M, Agha R. Health policy and leadership models during the COVID-19 pandemic: A review. Int J Surg. 2020; 81:122-129.
4. Zangrillo A, Beretta L, Silvani P, *et al.* Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: facing the COVID-19 pandemic emergency. Crit Care Resusc. 2020; 22:91-94.
5. Tsai TC, Jha AK, Gawande AA, Huckman RS, Bloom N, Sadun R. Hospital board and management practices are strongly related to hospital performance on clinical quality metrics. Health Aff. 2015; 34:1304-1311.
6. Marmo R, Nicolella M, Polverino F, Tibaut A. A methodology for a performance information model to support facility management. Sustainability. 2019; 11:7007.
7. McKee M, Edwards N, Atun R. Public–private partnerships for hospitals. Bull World Health Organ. 2006; 84:890-896.
8. Li L, Benton WC. Hospital capacity management decisions: emphasis on cost control and quality enhancement. Eur J Oper Res. 2003; 146:596-614.
9. Turkish Ministry of Health (MoH). Health Investments General Directorate. 2020. *https://sygm.saglik.gov.tr/TR,58066/3-yilda-10-sehir-hastanesi-hizmete-acildi.html* (accessed February 3, 2023). (in Turkish)
10. Top M, Sungur C. Opinions and evaluations of stakeholders in the implementation of the public-private partnership (PPP) model in integrated health campuses (city hospitals) in Turkey. Int J Health Plan Manag. 2019; 34:e241-e263.
11. Curtis JR, Kross EK, Stapleton RD. The importance of addressing advance care planning and decisions about do-not-resuscitate orders during novel coronavirus 2019 (COVID-19). JAMA. 2020; 323:1771-1772.
12. Ma X, Vervoort D. Critical care capacity during the COVID-19 pandemic: Global availability of intensive care beds. J Crit Care. 2020; 58:96-97.
13. Nayna Schwerdtle P, Connell CJ, Lee S, Plummer V, Russo PL, Endacott R, Kuhn L. Nurse expertise: A critical resource in the COVID-19 pandemic response. Ann Glob Health. 2020; 86:49.
14. Li LX, Benton WC, Leong K. The impact of strategic operations management decisions on community hospital performance. J Oper Manag. 2002; 20:389-408.
15. Yi P, George SK, Aliyas Paul J, Lin L. Hospital capacity planning for disaster emergency management. Socio-Economic Planning Sciences. 2010; 44:151-160.
16. Bouckaert N, Van den Heede K, Van de Voorde C. Improving the forecasting of hospital services: A comparison between projections and actual utilization of hospital services. Health Policy. 2018; 122:728-736.
17. McPake B, Hanson K. Managing the public–private mix to achieve universal health coverage. Lancet. 2016; 388:622-630.
18. Azcarate C, Esparza L, Mallor F. The problem of the last bed: Contextualization and a new simulation framework for analyzing physician decisions. Omega. 2020; 96: 1-20.
19. Gaughan J, Kasteridis P, Mason A, Street A. Why are there long waits at English emergency departments? Eur J Health Econ. 2019; 21:209-218.
20. Carrillo B, Feres J. Provider supply, utilization, and infant health: Evidence from a physician distribution policy. Am

Econ J Econ Policy. 2019; 11:156-196.
21. Morgan PA, Smith VA, Berkowitz TSZ, Edelman D, Van Houtven CH, Woolson SL, Hendrix CC, Everett CM, White BS, Jackson GL. Impact Of Physicians, Nurse Practitioners, And Physician Assistants On Utilization And Costs For Complex Patients. Health Aff (Millwood). 2019; 38:1028-1036.
22. Cartmill L, Comans TA, Clark MJ, Ash S, Sheppard L. Using staffing ratios for workforce planning: Evidence on nine allied health professions. Hum Resour Health. 2012; 10:2.
23. Thomas RK. Health services demand and utilization. in: health services planning. Springer, New York, 2021; pp.5-9.
24. Crisp N, Chen L. Global supply of health professionals. N Engl J Med. 2014; 370:950-957.
25. Fan EMP, Nguyen NHL, Ang SY, Aloweni F, Goh HQI, Quek LT, Ayre TC, Pourghaderi AR, Lam SW, Ong EHM. Impact of COVID-19 on acute isolation bed capacity and nursing workforce requirements: A retrospective review. J Nurs Manag. 2021; 29:1220-1227.
26. Goh KJ, Wong J, Tien JC, Ng SY, Duu Wen S, Phua GC, Leong CK. Preparing your intensive care unit for the COVID-19 pandemic: practical considerations and strategies. Crit Care. 2020; 24:215.
27. Adelaja I, Sayma M, Walton H, *et al.* A comprehensive hospital agile preparedness (CHAPs) tool for pandemic preparedness, based on the COVID-19 experience. Future Healthc J. 2020; 7:165-168.
28. Loayza NV. Costs and trade-offs in the fight against the COVID-19 Pandemic. World Bank Other Operational Studies 33764, No.35, The World Bank, US, 2020; pp.1-9.
29. Demirag I, Fırtın CE, Tekin Bilbil E. Managing expectations with emotional accountability: making City Hospitals accountable during the COVID-19 pandemic in Turkey. J. Public Budg. Account. Financ. Manag. 2020; 32:889-901.
30. Turkish Ministry of Health (MoH). Health Statistics Year Book. 2018. *https://dosyasb.saglik.gov.tr/Eklenti/36164,siy2018en2pdf.pdf?0* (accessed February 2, 2023).
31. Şahin MK, Aker S, Şahin G, Karabekiroğlu A. Prevalence of depression, anxiety, distress and insomnia and related factors in healthcare workers during COVID-19 pandemic in Turkey. J Community Health. 2020; 45:1168-1177.
32. Stock G, McDermott C. The effects of physicians on operational and financial performance in United States hospitals: staffing, human capital and knowledge spillovers. Int J Oper Prod. (ahead-of-print). 2023. *https://www.emerald.com/insight/content/doi/10.1108/IJOPM-07-2022-0457/full/html* (accessed February 1, 2023).
33. Mattiuzzi C, Lippi G, Henry BM. Healthcare indicators associated with COVID-19 death rates in the European Union. Public Health. 2021; 193:41-42.
34. Liu J, Eggleston K. The association between health workforce and health outcomes: A cross-country econometric study. Soc Indic Res. 2022; 163:609-632.
35. Kuntz L, Scholtes S, Vera A. Incorporating efficiency in hospital-capacity planning in Germany. Eur J Health Econ. 2007; 8:213-223.
36. Chen L, Evans T, Anand S, *et al*. Human resources for health: overcoming the crisis. Lancet. 2004; 364:1984-1990.
37. Forster AJ, Stiell I, Wells G, Lee AJ, van Walraven C. The effect of hospital occupancy on emergency department length of stay and patient disposition. Acad Emerg Med. 2003; 10:127-133.
38. Harrison GW, Shafer A. Modelling variability in hospital bed occupancy. Health Care Manag Sci. 2005; 8:325-334.
39. Roemer MI. Hospital utilization and the supply of physicians. JAMA. 1961; 178:989-993.
40. Traczynski J, Udalova V. Nurse practitioner independence, health care utilization, and health outcomes. J Health Econ. 2018; 58:90-109.
41. Maier CB, Batenburg R, Birch S, Zander B, Elliott R, Busse R. Health workforce planning: which countries include nurse practitioners and physician assistants and to what effect? Health Policy. 2018; 122:1085-1092.
42. Basu S, Berkowitz SA, Phillips RL, Bitton A, Landon BE, Phillips RS. Association of primary care physician supply with population mortality in the United States, 2005-2015. JAMA Intern Med. 2019; 179:506-514.
43. Jee M, Or Z. Health outcomes in OECD countries: a framework of health indicators for outcome-oriented policymaking. OECD Labour Market and Social Policy Occasional Papers, No. 36, OECD Publishing, Paris, 1999. *https://doi.org/10.1787/513803511413* (accessed February 4, 2023).
44. Ricketts TC, Holmes GM. Mortality and physician supply: does region hold the key to the paradox? Health Serv Res. 2007; 42:2233-2251.
45. Tourangeau AE, Cranley LA, Jeffs L. Impact of nursing on hospital patient mortality: a focused review and related policy implications. Qual Saf Health Care. 2006; 15:4-8.
46. Bentler PM. Comparative fit indexes in structural models. Psychol Bull. 1990; 107:238-246.
47. Kline RB. Principles and practice of structural equation modeling (2nd ed.). Guilford Press. New York, US, 2005; pp.270-272.
48. Hooper D, Coughlan J, Mullen M. Structural equation modelling: guidelines for determining model fit. Electron J Bus Res. 2008; 6:53-60.
49. Turkish Ministry of Health (MoH). Health Statistics Year Book. 2020. *https://dosyasb.saglik.gov.tr/Eklenti/43400,siy2020-eng-26052022pdf.pdf?0* (accessed February 3, 2023).

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Evaluation of a bundle approach for the prophylaxis of ventilator-associated pneumonia: A retrospective single-center Study

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Abstract: Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring after the first 48 hours of intubation and mechanical ventilation and is the most frequent hospital-acquired infection associated with intensive care unit (ICU) admissions. Herein, we defined a novel VAP bundle including 10 preventive items. We analyzed compliance rates and clinical effectiveness associated with this bundle in patients undergoing intubation at our medical center. A total of 684 consecutive patients who underwent mechanical ventilation were admitted to the ICU between June 2018 and December 2020. VAP was diagnosed by at least two physicians based on the relevant United States Centers for Disease Control and Prevention criteria. We retrospectively evaluated associations between compliance and VAP incidence. The overall compliance rate was 77%, and compliance generally remained steady during the observation period. Moreover, although the number of ventilatory days remained unchanged, the incidence of VAP improved statistically significantly over time. Low compliance was identified in four categories: head-of-bed elevation of 30-45º, avoidance of oversedation, daily assessment for extubation, and early ambulation and rehabilitation. The incidence of VAP was lower in those with an overall compliance rate of ≥ 75% than its incidence in the lower compliance group (15.8 *vs.* 24.1%, $p = 0.018$). When comparing low-compliance items between these groups, we found a statistically significant difference only for daily assessment for extubation (8.3 *vs.* 25.9%, $p = 0.011$). In conclusion, the evaluated bundle approach is effective for the prophylaxis of VAP and is thus eligible for inclusion in the Sustainable Development Goals.

***Keywords*:** intensive care unit, intratracheal intubation, mechanical ventilation

Introduction

Ventilator-associated pneumonia (VAP) is a preventable iatrogenic complication that can develop in patients undergoing mechanical ventilation. VAP is the most frequent hospital-acquired infection occurring in the intensive care unit (ICU) and has a high associated mortality rate (*1*). More specifically, the mortality rate for VAP ranges from 24-51% according to previously published findings (*2*).

The prevention of VAP has great value in the management of mechanical ventilation with intratracheal intubation. In addition to the personal, familial, and societal burden of this disease, past reports have demonstrated that VAP increases the length of hospital stay as well as costs associated with treatment and care and the usage of antibiotics in patients with longer hospital stays (*3-6*). It is therefore necessary to avert the risks of respiratory management in this setting and to prevent pathogens from entering the lower respiratory tract from both external and internal sources.

Preventive bundle approaches reduce the incidence of VAP. However, VAP prevention bundles are composed of different items and may vary substantially between institutions. Each item considered for the prevention of VAP (*i.e.*, included in the VAP prevention bundle) in the present study has been extensively studied in prior work (*7-9*). Some items in the VAP prevention bundle, including hand hygiene, oral care, and subglottic suctioning of secretions from the upper cuff, are effective in preventing the invasion of pathogens from outside the tube. Other measures aim to prevent pathogen invasion from inside the tracheal tube, including the use of closed suction circuits and the use of disposable breathing circuits.

For the above mentioned reasons, it is highly important to establish effective preventive strategies for VAP (*10*). However, the generalizability of prior work

and the effectiveness of the specific bundle approach presented herein remains unclear. In the present study, we comprehensively examined the preventive efficacy of a VAP prevention bundle consisting of ten items that had been implemented at our medical center.

Materials and Methods

This study was approved by the ethical review board at the National Center for Global Health and Medicine on September 10, 2021 (approval number: NCGM-S-004300-00). The requirement for written informed consent was waived due to the retrospective design of this study. This work was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013).

Patient selection and diagnosis of VAP

All patients who were admitted to the general ICU at our institution between June 2018 to December 2020, were older than 20 years of age, and received intubated mechanical ventilation for more than 48 hours were eligible for inclusion. We included 1,903 patients who were admitted to our ICU.

We use the following artificial respirators at our department: the Dräger Evita® Infinity V500 (Dräger, Lübeck, Germany) and the Nihon Kohden® HAMILTON-G5 (Nihon Kohden, Tokyo, Japan). In addition, was the Taper Guard® Evac (Medtronic, Dublin, Ireland) the tracheal intubation tube used herein; this tube uses subglottic suctioning.

VAP was evaluated based on the diagnostic criteria for clinically defined pneumonia delineated by the United States (US) Centers for Disease Control and Prevention (*1*). The infection control team, radiology department, and ICU physicians at our medical center screened suspected cases of VAP, and the supervising ICU specialist made a final diagnosis of VAP based on chest imaging test results, clinical signs/symptoms, and laboratory findings. We evaluated the severity of all VAP patients using sequential organ failure assessment (SOFA) scores at ICU admission and on ICU discharge (*11*).

Bundle implemented at our institution

The VAP prevention bundle evaluated in the current study consisted of the following ten items (Supplemental Figure S1); *i*) hand hygiene, *ii*) head-of-bed elevation (30-45º), *iii*) oral care with cetylpyridinium chloride (CPC), *iv*) avoidance of oversedation, *v*) proper breathing circuit management, *vi*) appropriate maintenance of endotracheal tube cuff pressure, *vii*) closed system and subglottic suctioning, *viii*) daily assessment for extubation, *ix*) early ambulation and rehabilitation, and *x*) peptic ulcer and deep vein thrombosis (DVT) prophylaxis. We modified the bundles implemented in studies conducted by the US Institute for Healthcare Improvement (IHI) and the Japanese Society of Intensive Care Medicine (*12,13*) based on the current evidence base and an evolving clinical situation (*14,15*). For example, we added "maintenance of adequate cuff pressure (20-30 cmH_2O)", "use of a tracheal tube with aspiration of subglottic secretions", and "early ambulation and rehabilitation" items to the bundle.

Bundle compliance rates were calculated using the VAP care bundle sheet included in patients' medical records and were entered into database software (FileMaker Pro, version 19, Claris International Inc. Cupertino, CA, USA) for subsequent analyses.

Statistical analyses

Differences in categorical variables were analyzed using Chi-square tests, whereas continuous variables were analyzed using *t*-tests. All cumulative survival curves were estimated using the Kaplan-Meier method. Intergroup differences were evaluated using log-rank tests.

The VAP incidence was calculated by dividing the number of VAP cases by the total number of ventilator-days and multiplying the result by 1,000 (*1*). Hypothesis testing regarding differences in the incidence of VAP was conducted to compare the pre- and post-intervention VAP incidence rates using z-scores. We considered two-sided *p*-values of < 0.05 as the threshold for statistical significance. All statistical analyses were performed using the R statistical software (ver. 3.0.2, The R Project for Statistical Computing, Vienna, Austria. *http://www.r-project.org*).

Results

Among the 1,903 included patients, 684 (36%) received mechanical ventilation. The clinical characteristics of the patients in the intubation and non-intubation groups are shown in Table 1. The intubation group included 406 (59%) men and the median age at the time of admission was 64 years (standard deviation, ± 17 years). The patients in the intubation group had mean SOFA scores of 7.1 ± 3.4 on admission and 4.9 ± 3.8 at discharge, respectively. The median length of patients' ICU stays was 8.2 ± 7.0 days. Forty-eight patients died in the ICU in the intubation group and the overall mortality rate was 7.0%.

The reasons for ICU admission are described in Table 1. In the intubation group, gastrointestinal surgery exhibited the highest frequency (181 patients, 26.5%), followed by cardiovascular surgery (114 patients, 16.7%). In terms of types of admission, emergency surgery exhibited the highest frequency (369 patients, 53.9%), followed by scheduled surgery (184 patients, 26.9%).

Compliance rates for the VAP bundle and the VAP incidence

The compliance rate for each item is shown in Figure 1. In our ICU, we routinely implement several items as part of our standard of care: hand hygiene (*i*), oral care with CPC (*iii*), proper breathing circuit management (*v*), appropriate maintenance of endotracheal tube cuff pressure (*vi*), and peptic ulcer and DVT prophylaxis (*x*). The compliance rate was 100% for each item.

Subglottic suction (*vii*) was not implemented in only a few emergency surgery cases, and hence this preventive measure achieved a compliance rate of 92.6%. Conversely, we could not implement early ambulation and rehabilitation (*ix*) effectively, and the compliance rate for this preventive measure reached only 5.8%. The compliance rates for the remaining three measures (*ii*, *iv*, and *viii*) were each approximately 50%. Reasons for these findings included restrictions on therapeutic management, decreased levels of consciousness, and unstable vital signs. The total compliance rate for the ten measures comprising the VAP prevention bundle was 77.0%.

Ventilator-days and VAP incidence in the intubation group are shown in Figure 2. In Japan, ventilator-days increased considerably in April 2020 due to the coronavirus disease 2019 pandemic. This time period represented the start of the pandemic in Japan and the uptick in this metric might have occurred due to evolving surveillance and treatment methods. However, the number of ventilator-days was almost unchanged in every other month, and the median number of ventilator-days was 6.17 days (Figure 2A).

Although VAP incidence varied each month (ranging from 0.0 to 96.2 per 1,000 ventilator-days), it gradually decreased from 2018 to 2020. The total VAP incidence was 31.5 per 1,000 ventilator-days during the observation period (Figure 2B).

Prophylaxis effects based on compliance rates for the VAP bundle

Table 1. Characteristics of ventilated and non-ventilated patients, June 2018 to December 2020

Variable	Intubated	Non-intubated
Patients receiving MV, *n*	684	1,219
Male sex, *n* (%)	406 (59.3)	779 (63.9)
Age, mean ± SD	63.9 ± 17.2	66.9 ± 14.5
SOFA score on ICU admission, mean ± SD	7.1 ± 3.4	2.3 ± 2.1
SOFA score at ICU discharge, mean ± SD	4.9 ± 3.8	1.6 ± 1.9
ICU length of stay (days), mean ± SD	8.2 ± 7.0	2.7 ± 1.6
ICU mortality (%)	48 (7.0)	7 (0.6)
Underlying disease, *n* (%)		
Gastrointestinal surgery	181 (26.5)	484 (39.7)
Cardiovascular surgery	114 (16.7)	105 (8.6)
Respiratory surgery	5 (0.7)	294 (24.1)
Neurosurgery	240 (35.1)	144 (11.8)
Other surgery	13 (1.9)	24 (2.0)
Emergency and critical care medicine	26 (3.8)	2 (0.2)
Internal medicine	51 (7.5)	24 (2.0)
Cardiovascular medicine	51 (7.5)	142 (11.6)
Pediatrics	3 (0.4)	0 (0)
Type of admission, *n* (%)		
Scheduled surgery	184 (26.9)	934 (76.6)
Emergency surgery	369 (53.9)	117 (9.6)
Coronary intervention	21 (3.1)	104 (8.5)
Medical	110 (16.1)	64 (5.3)
Trauma	41 (6.0)	15 (1.2)

ICU, intensive care unit; MV, mechanical ventilation; SD, standard deviation; SOFA, sequential organ failure assessment.

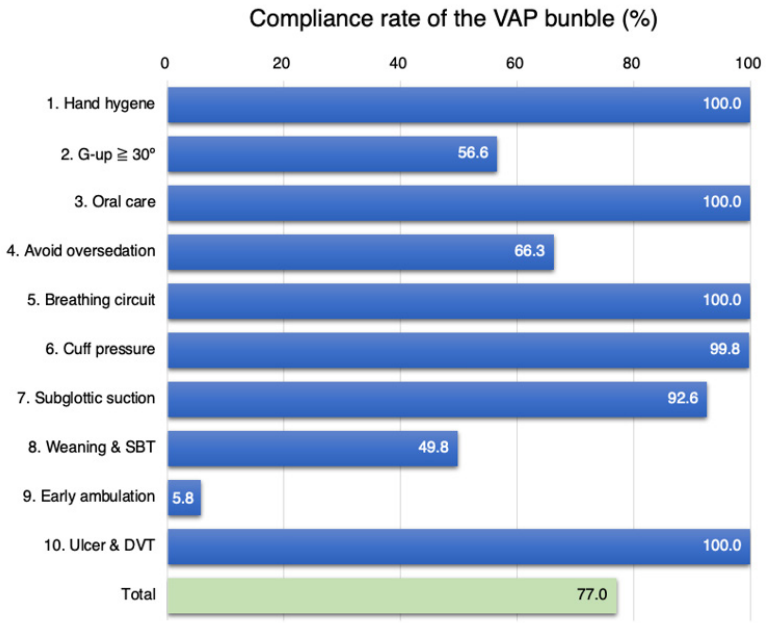

Figure 1. Compliance rate of the VAP bundle. SBT, spontaneous breathing trial; DVT, deep vein thrombosis.

According to the total compliance rate of 77.0% reported above, the 684 patients who required mechanical ventilation were divided into two groups using a cut-off value of 75%. The evaluated clinical outcomes included the incidence of VAP, as shown in Table 2, as well as associated mortality rates.

Regarding total compliance rates, the high compliance group comprised 385 patients (56%) with a compliance rate of ≥ 75%, whereas the low compliance group comprised 299 (44%) with a compliance rate of < 75%; 61 (15.8%) developed VAP in the high compliance group, in contrast with 72 (24.1%) in the low compliance group. We observed statistically significant differences in the proportion of VAP occurrence between the two groups ($p = 0.02$, Figure 3A).

Moreover, 11 patients (2.9%) died in the high compliance group, in contrast with 37 (12.4%) who died in the low compliance group ($p < 0.001$, Figure 3B). Relationships between the incidence of VAP and the bundle items with low compliance rates (*ii*, *iv*, *viii*, and *ix*) are presented in Figure 4.

Only daily assessment for extubation (*viii*) demonstrated statistically significant differences with regard to the proportion of VAP cases; the high compliance group included 252 patients (37%) and the low compliance group included 432 (63%). A total of 21 patients (8.3%) developed VAP in the high compliance group, whereas 112 (25.9%) developed VAP in the low compliance group ($p = 0.011$, Figure 4C, Table 2). No other items exhibited statistically significant differences.

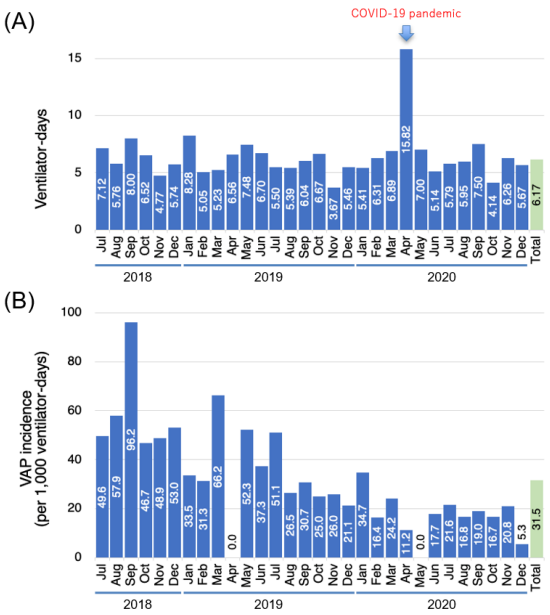

Figure 2. Number of ventilator-days and VAP incidence during the observation period. (A) The number of ventilator-days, **(B)** VAP incidence (per 1,000 ventilator-days). VAP, ventilator-associated pneumonia.

Discussion

In the present study, patients with high compliance rates for the evaluated VAP prevention bundle demonstrated a lower incidence of VAP than the VAP incidence of those with low compliance rates (Figure 3). Daily assessment for extubation (*viii*) affected the incidence of VAP, such that those with high compliance showed a lower incidence of VAP than those in the low compliance group (Figure 4C). However, no other items showed statistically significant differences.

In this study, the intubation group included patients with various risk factors and profiles, such as high SOFA scores, an increased length of hospital stay, and high mortality rates (Table 1). Risk factors increasing the incidence of VAP have been reported in many prior reports, and include long-term intubation, disorders of

Table 2. Clinical outcomes as relevant to the ventilator-associated pneumonia (VAP) prevention bundle evaluated at our medical center

VAP bundle items	Patients (*n*)	VAP (*n*)	ICU-days	Ventilator-days	VAP (%)	VAP incidence (per 1,000 MV days)	*p*-value*
Total compliance							
High (compliance ≥ 75%)	385	61	9.13	6.49	15.8	24.4	0.018
Low (compliance < 75%)	299	72	6.91	5.74	24.1	42.0	
Gatching up the bed to 30-45º							
High (compliance ≥ 75%)	330	60	9.34	6.59	18.2	27.6	0.545
Low (compliance < 75%)	354	73	7.06	5.77	20.6	35.7	
Avoidance of oversedation							
High (compliance ≥ 75%)	378	61	7.89	5.59	16.1	28.9	0.217
Low (compliance < 75%)	306	72	8.49	6.88	23.5	34.2	
Daily assessments for extubation							
High (compliance ≥ 75%)	252	21	6.65	4.10	8.3	20.3	0.011
Low (compliance < 75%)	432	112	9.04	7.37	25.9	35.2	
Early ambulation and rehabilitation							
High (compliance > 0%)	76	27	16.17	13.67	35.5	26.0	0.900
Low (0% compliance)	608	106	7.16	5.23	17.4	33.3	
Total	684	133	8.16	6.17	19.4	31.5	

ICU, intensive care unit; MV, mechanical ventilation. *Generalized Wilcoxon test.

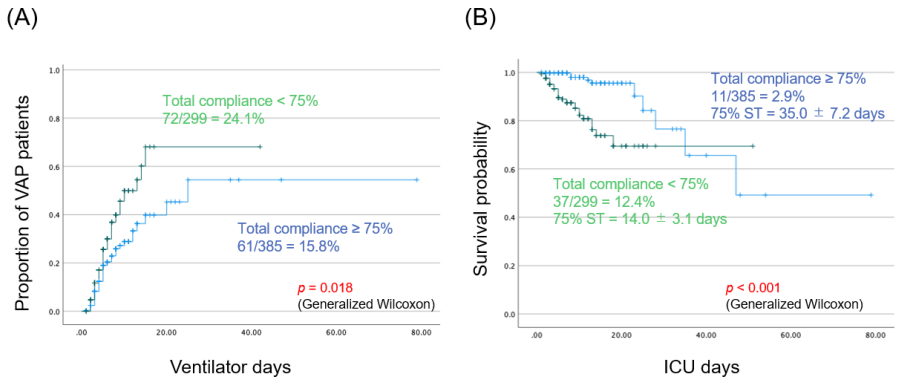

Figure 3. Proportion of VAP occurrence according to the compliance rate. (A) Proportion of VAP patients, **(B)** Survival probability. VAP, ventilator-associated pneumonia.

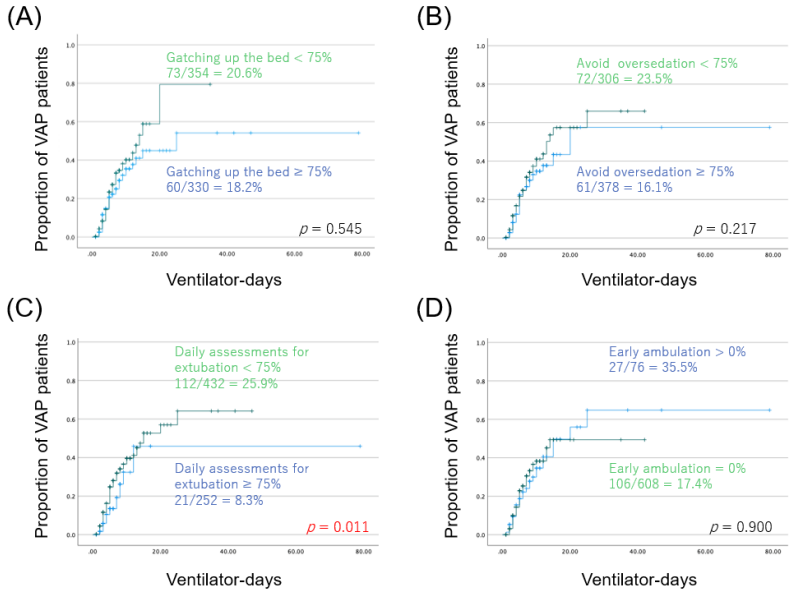

Figure 4. Proportion of VAP occurrence according to the preventive item. (A) Gatching up the bed, **(B)** Avoid oversedation, **(C)** Daily assessments for extubation, **(D)** Early ambulation. VAP, ventilator-associated pneumonia.

consciousness, and various comorbidities (*16-18*). We introduced the bundle approach described herein to at-risk patients with the aim of preventing VAP.

In consideration of such risk factors, the US IHI and the Japanese Society of Intensive Care Medicine have included item x (*i.e.*, the peptic ulcer and DVT prophylaxis item) in their protocols. In Japan, the incidence rates of obesity and pulmonary embolism are lower than the respective incidence of each condition in the US (*12,13*). Hence, DVT prophylaxis has less clinical importance in Japan than it does in the US, and we conclude that preventive measures should be modified based on the clinical situation specific to each institution. The incidence of VAP gradually decreased after the introduction of our modified bundle (Figure 2). We emphasize that our selected measures led to good clinical outcomes overall.

The favorable consequences of including an educational program were proven in a past study, in which the resulting incidence of VAP was reduced by 51% (*2*). In this study, the incidence of VAP has decreased over time due to better management (overall and for each preventive measure included in the bundle) as compared with our management capabilities immediately after the introduction of the preventive bundle. One potential reason for this may be that the level of nursing care has improved over time because nurses' awareness of and training regarding VAP care has increased.

Our department was able to comply with many of the measures implemented in the evaluated preventive bundle, hence yielding a median compliance rate of

77%. This higher compliance rate led to a lower VAP incidence. Moreover, a subgroup analysis of the four measures with the lowest compliance rates showed that only daily assessment for extubation (item *viii*) was statistically significantly different between compliance groups. Prior studies have reported that early extubation is difficult in older patients as well as in patients in poor general condition and/or with consciousness disorders due to brain injury (*19,20*). Invasive surgery for older patients and those with cerebrovascular disease may lead to prolonged intubation, even at our institution. In these cases, tracheostomy and aggressive nutritional management may reduce the occurrence of VAP (*21,22*). We would also like to consider tracheostomy for long-term management in future research.

In the preventive bundle evaluated herein, "early ambulation and rehabilitation" was the only item that showed low compliance rates. The clinical effects of early ambulation and rehabilitation have been proven (*23,24*). We aim to identify the factors contributing to inadequate management as well as to improve management methods in future work. We also note that our medical staff has experienced some difficulty implementing ambulation and rehabilitation programs in normally intubated patients (other than tracheostomy patients) due to bucking and blood pressure fluctuations, which may occur given inadequate sedation. In our ICU, we try to achieve a 90° gatch-up position or a standing position using a Sara® Combilizar device (Arjo, Stockholm, Sweden) under mild sedation. We hope to increase the number of cases undergoing therapeutic ambulation and rehabilitation protocols in the future.

Our study had several limitations. First, this was a retrospective study that only included Japanese patients from a single institution. However, our database is large and has been continuously updated based on uniform follow-up protocols. Second, although a general rule was similarly applied to all patients when diagnosing VAP, the diagnostic criteria for VAP are somewhat controversial. For example, criteria that have been considered for VAP diagnoses (and remain controversial) include evaluation of the patient's respiratory condition (*i.e*., based on the fraction of inspired oxygen and positive-end-expiratory pressure findings) (*1*). Third, according to the diagnostic criteria for VAP described above, we evaluated respiratory function and symptoms in reaching VAP diagnoses; however, the data for bacterial composition in mechanical ventilation patients' sputum tests included many missing values. Fourth, we could not identify survival effects for VAP. No patient died from VAP in this study; the main cause of death in our ICU was primary disease or other severe complications thereof. A multicenter prospective study is required for confirming the efficacy of the VAP bundle approach in intubated patients admitted to the ICU.

In conclusion, an observed decreased incidence of VAP was a critically important outcome of the VAP bundle approach in the intubated patients evaluated herein. We plan to enact these preventive measures at our medical center using this VAP bundle. This approach was effective for the prophylaxis of VAP and is hence eligible for inclusion in our Sustainable Development Goals.

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

References

1. National Healthcare Safety Network. Ventilator-associated (VAP) and Non-ventilator-associated Pneumonia (PNEU) Event. 2021. *https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf* (accessed April 25, 2022)
2. Salahuddin N, Zafar A, Sukhyani L, Rahim S, Noor MF, Hussain K, Siddiqui S, Islam M, Husain SJ. Reducing ventilator-associated pneumonia rates through a staff education programme. J Hosp Infect. 2004; 57:223-227.
3. Rosenthal VD. Health-care-associated infections in developing countries. Lancet. 2011; 377:186-188.
4. Melsen WG, Rovers MM, Groenwold RH, *et al*. Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis. 2013; 13:665-671.
5. Alp E, Kalin G, Coskun R, Sungur M, Guven M, Doganay M. Economic burden of ventilator-associated pneumonia in a developing country. J Hosp Infect. 2012; 81:128-130.
6. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol. 2012; 33:250-256.
7. Abbott CA, Dremsa T, Stewart DW, Mark DD, Swift CC. Adoption of a ventilator-associated pneumonia clinical practice guideline. Worldviews Evid Based Nurs. 2006; 3:139-152.
8. Jadot L, Huyghens L, De Jaeger A, *et al*. Impact of a VAP bundle in Belgian intensive care units. Ann Intensive Care. 2018; 8:65.
9. Sousa AS, Ferrito C, Paiva JA. Application of a ventilator associated pneumonia prevention guideline and outcomes: A quasi-experimental study. Intensive Crit Care Nurs. 2019; 51:50-56.
10. Xie J, Yang Y, Huang Y, *et al.* The current epidemiological landscape of ventilator-associated pneumonia in the intensive care unit: A multicenter prospective observational study in China. Clin Infect Dis. 2018; 67:S153-S161.
11. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive

Care Medicine. Crit Care Med. 1998; 26:1793-1800.
12. Institute for Healthcare Improvement. How-to Guide: Prevent Ventilator-Associated Pneumonia. 2005. *http://www.ihi.org/resources/Pages/Tools/HowtoGuidePreventVAP.aspx* (accessed April 25, 2022)
13. The Japanese Society of Intensive Care Medicine. Ventilator-Associated Pneumonia Prevention Bundle (VAP Bundle). 2010. *https://www.jsicm.org/pdf/2010VAP.pdf* (accessed April 25, 2022). (in Japanese)
14. Eom JS, Lee MS, Chun HK, Choi HJ, Jung SY, Kim YS, Yoon SJ, Kwak YG, Oh GB, Jeon MH, Park SY, Koo HS, Ju YS, Lee JS. The impact of a ventilator bundle on preventing ventilator-associated pneumonia: A multicenter study. Am J Infect Control. 2014; 42:34-37.
15. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36:309-332.
16. Wu D, Wu C, Zhang S, Zhong Y. Risk factors of ventilator-associated pneumonia in critically ill patients. Front Pharmacol. 2019; 10:482.
17. Jaffal K, Six S, Zerimech F, Nseir S. Relationship between hyperoxemia and ventilator associated pneumonia. Ann Transl Med. 2017; 5:453.
18. Wałaszek M, Kosiarska A, Gniadek A, Kołpa M, Wolak Z, Dobroś W, Siadek J. The risk factors for hospital-acquired pneumonia in the intensive care unit. Przegl Epidemiol. 2016; 70:15-20, 107-110.
19. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med. 2000; 161:1530-1536.
20. Lai CC, Chen CM, Chiang SR, Liu WL, Weng SF, Sung MI, Hsing SC, Cheng KC. Establishing predictors for successfully planned endotracheal extubation. Medicine. 2016; 95:e4852.
21. Chorath K, Hoang A, Rajasekaran K, Moreira A. Association of early vs late tracheostomy placement with pneumonia and ventilator days in critically ill patients: A meta-analysis. JAMA Otolaryngol Head Neck Surg. 2021; 147:450-459.
22. Ścisło L, Walewska E, Bodys-Cupak I, Gniadek A, Kózka M. Nutritional status disorders and selected risk factors of ventilator-associated pneumonia (VAP) in patients treated in the intensive care ward - A retrospective study. Int J Environ Res Public Health. 2022; 19:602.
23. Girard TD, Alhazzani W, Kress JP, *et al.* An official American Thoracic Society/American College of Chest Physicians clinical practice guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Resp Crit Care Med. 2017; 195:120-133.
24. Schweickert WD, Pohlman MC, Pohlman AS, *et al.* Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. Lancet. 2009; 373:1874-1882.

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Supplementary Data

Supplemental Figure S1. Graphic symbol of ten items in VAP bundle. VAP, ventilator-associated pneumonia.

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Comparative analysis of the outcomes of gastrectomy *vs.* endoscopic mucosal resection or endoscopic submucosal dissection for the treatment of gastric tube cancer after esophagectomy

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Abstract: This study investigated the clinical characteristics of patients with gastric tube cancer following esophagectomy at our hospital, and to examine the outcomes of gastrectomy versus endoscopic submucosal dissection. Of 49 patients who underwent treatment for gastric tube cancer that developed 1 year or more after esophagectomy, 30 patients underwent subsequent gastrectomy (Group A), and 19 patients underwent endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) (Group B). The characteristics and outcomes of these two groups were compared. The interval between esophagectomy and diagnosis of gastric tube cancer ranged from 1 to 30 years. The most common location was the lesser curvature of the lower gastric tube. When the cancer was detected early, EMR or ESD was performed, and the cancer did not recur. In advanced tumors, gastrectomy was performed but the gastric tube was difficult to approach and lymph node dissection was difficult; two patients died as a result of the gastrectomy. In Group A, recurrence occurred most often as axillary lymph node, bone, or liver metastases; in Group B, no recurrence or metastases were observed. In addition to recurrence and metastasis, gastric tube cancer is often observed after esophagectomy. The present findings highlight the importance of early detection of gastric tube cancer after esophagectomy and that the EMR and ESD procedures are safe and have significantly fewer complications compared with gastrectomy. Follow-up examinations should be scheduled with consideration given to the most frequent sites of gastric tube cancer occurrence and the time elapsed since esophagectomy.

***Keywords*:** gastrectomy, endoscopic submucosal resection, long-term follow-up after esophagectomy, metachronous cancer

Introduction

Esophageal cancers are squamous cell carcinomas or adenocarcinomas that occur in the esophagus. In the past, the prognosis of patients with esophageal cancer was very poor (*1*), but the introduction of a multidisciplinary treatment approach and advanced surgical techniques such as thoracoscopic surgery and robot-assisted esophagectomy have greatly improved therapeutic outcomes. However, there has been a marked increase in the rates of diagnosis of metachronous cancer after the initial esophagectomy (current incidence reported in the literature 11.3%–12%) (*2-5*).

In our hospital in Japan, we have found that metachronous cancer is diagnosed prior to esophagectomy in 6.4% of cases, at the same time as esophagectomy in 4.8% of cases, and after esophagectomy in 12.8% of cases (data not shown). These metachronous cancers are diagnosed most frequently in the oropharynx, hypopharynx, and larynx, which are regions covered by squamous epithelium (*5*), followed by the gastric tube, which is the reconstructed esophagus following esophagectomy (*3-5*). The surgical approach for the resection of gastric tube cancer depends on the reconstruction route used for the prior esophagectomy. If the route used for the reconstruction was the intrathoracic route, the surgery is more invasive than the antethoracic route. Because its route was not necessary to perform thoracotomy. Although the incidence of esophageal cancer is increasing worldwide (*6*), much remains unknown about gastric tube cancer following esophagectomy, such as the common sites of occurrence, patterns of metastasis, most effective treatment methods and follow-up schedules.

Here, we investigated the clinical characteristics of patients with gastric tube cancer following esophagectomy at our hospital and examined the outcomes of gastrectomy versus endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

Patients and Methods

Study design

This was a retrospective study conducted at the Department of Surgery, Institute of Gastroenterological Surgery, Tokyo Women's Medical University, Japan. From 1964 to 2012, a total of 2,908 patients underwent radical esophagectomy and esophageal reconstruction at our institute. Of these 2,908 patients, 49 developed gastric tube cancer 1 year or more after esophagectomy and underwent treatment for gastric tube cancer between 1970 and 2020. In the present study, these 49 patients were divided into two groups based on the treatment they received for the gastric tube cancer: 30 patients underwent gastrectomy and were assigned to Group A, and 19 patients underwent endoscopic treatment (EMR or ESD) and were assigned to Group B. The indications for endoscopic mucosal resection EMR or ESD were the same as for gastric cancer, well-differentiated adenocarcinoma (G1); depth of invasion limited to the lamina propria; less than 2.0 cm in diameter; and no ulceration. However, ESD is expanding indications excluding size. Surgery for the treatment of gastric tube cancer was excluded when there was invasion of other organs (T4) or recurrence in other organs (M1).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Tokyo Women's Medical University, Approval No. 4582). Informed consent and consent for publication were obtained from all subjects involved in the study.

Statistical analyses

All data are presented as the medians and total ranges unless otherwise stated. Survival was calculated using the Kaplan–Meier method and then compared between groups with the log-rank test. The hazard ratio of survival was calculated with Cox proportional hazard analyses. A p value < 0.05 was statistically significant.

Results

Patient characteristics

Table 1 shows the clinical characteristics of the patients at the time of esophagectomy. 37% in Group A or 37% in Group B were diagnosed Stage I. Lymph node metastasis occurred in 47% in Group A or 58% in Group B. The most common reconstruction route was the antesternal route in Group A, and the posterior mediastinal route in Group B. Neither group received much adjuvant therapy. There were no differences between Group A and Group B except for reconstruction route.

Table 2 shows the clinical characteristics of the patients at the time of diagnosis of gastric tube cancer. Table 3 shows the gastric tube cancer symptoms reported by the patients and the means of detection of the cancer. In Group A, the gastric tube cancer was not diagnosed until it was in an advanced state in 67% and was detected by palpation in 33% of patients; these findings were attributed to the use of the antesternal route of gastric tube reconstruction and to the fact that in the past the intervals between follow-up examinations were longer. In Group B, there were no symptoms because all cancers were discovered in an early stage *via* endoscopy. Because most cancers in Group A were advanced, symptoms at detection included passage obstruction, palpation, and pain. In Group B, all patients were asymptomatic. 55% in the gastric tube cancer was located in the lower gastric tube and 35% was located at the site sutured to form the gastric tube (the resected side of the lesser curvature side). The most common macroscopic classifications of early-stage cancers in Group A and Group B were 0-IIc and 0-IIa, respectively. In Group A, lymph node metastasis, lymphatic vessel invasion, or vascular invasion were observed at similar rates; in Group B no such metastasis or invasion was observed. Histologically, 33% of cases in Group A were poorly differentiated, whereas there was no poorly differentiated cases in Group B. Multiple gastric tube cancers developed in four patients in Group A and in one patient in Group B.

Table 1. Characteristics of the patients at the time of esophagectomy

Parameter	Gastrectomy (n = 30) Group A	EMR or ESD (n = 19) Group B
Mean age at the time of esophagectomy	60.5	64.5
Gender (M/F)	(29 / 1)	(19 / 0)
Location of esophageal cancer (Ut / Mt / Lt / unknown)	(3 / 20 / 5 / 2)	(3 / 10 / 6 / 0)
Depth (T1a / T1b / T2 / T3 / T4 / unknown)	(2 / 9 / 5 / 10 / 0 / 4)	(1 / 6 / 1 / 10 / 1 / 0)
Lymph node metastasis (N0 / N1 / unknown)	(12 / 14 / 4)	(8 / 11 / 0)
Stage (I / II / III / IVa / unknown)	(11 / 5 / 11 / 0 / 3)	(7 / 2 / 9 / 1 / 0)
Reconstruction route (antesternal / retrosternal / posterior mediastinal)	(21 / 5 / 4)	(3 / 2 / 14)
Adjuvant therapy for esophageal cancer (+ / - / unknown)	(6 / 20 / 4)	(3 / 15 / 1)

This criteria is in accordance with the Japanese Classification of Esophageal Cancer 11th 2015 by the Japan Esophageal Society. EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection, Ut: upper thoracic esophagus, Mt: middle thoracic esophagus, Lt: lower thoracic esophagus. T1a: Tumor confined to the mucosa (M). T1b: Invasion to but not beyond the submucosa (SM). T2: Invasion to but not beyond the muscularis propria (MP). T3: Invasion to the esophageal adventitia (Ad). T4: Invasion to the adjacent organs (Adj).

Table 2. Characteristics of the patients at the time of diagnosis of gastric tube cancer

Parameter	Gastrectomy (n = 30) Group A	EMR or ESD (n = 19) Group B
Mean age at the time of diagnosis	70.3	67.1
Gender (M/F)	(29 / 1)	(19 / 0)
Location on gastric tube (Upper / middle / lower / unknown)	(4 / 7 / 16 / 3)	(0 / 5 / 11 / 3)
Location of gastric tube (GC / LC / AW / PW / all / unknown)	(2 / 11 / 7 / 3 / 1 / 3)	(2 / 6 / 3 / 5 / 0 / 3)
Macroscopic Classification (0-I / 0-IIa / 0-IIb / 0-IIc / 1 / 2 / 3 / 4 / unknown)	(1 / 4 / 1 / 7 / 3 / 1 / 4 / 5 / 4)	(3 / 10 / 1 / 2 / 0 / 0 / 0 / 0 / 3)
Depth (m / sm / mp / ss / se / si / unknown)	(4 / 6 / 4 / 4 / 10 / 0 / 2)	(16 / 1 / 0 / 0 / 0 / 0 / 2)
Lymph node metastasis (n0 / n1 / no lymphadenectomy / unknown)	(9 / 7 / 9 / 5)	(0 / 0 / 14 / 5)
Lymphatic vessel invasion (0 / 1 / 2 / 3 / unknown)	(9 / 8 / 7 / 1 / 5)	(16 / 0 / 0 / 0 / 3)
Vascular invasion (0 / 1 / 2 / 3 / unknown)	(13 / 6 / 5 / 1 / 5)	(16 / 0 / 0 / 0 / 3)
Stage (I / IIA / IIB / III / unknown)	(13 / 1 / 5 / 8 / 3)	(16 / 0 / 0 / 0 / 3)
Histology (well / mod / poorly / unknown)	(10 / 6 / 10 / 4)	(15 / 1 / 0 / 3)
Double cancer (+ / − / unknown)	(4 / 23 / 3)	(1 / 15 / 3)

This criteria is in accordance with the Japanese classification of gastric carcinoma: 3rd English edition (2011) by the Japanese Gastric Cancer Association (JGCA). GC: greater curvature, LC: lesser curvature, AW: anterior wall, PW: posterior wall, EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection. T1a: Tumor confined to the mucosa (M). T1b: Tumor confined to the submucosa (SM). T2: Tumor invades the muscularis propria (MP). T3: Tumor invades the subserosa (SS). T4: Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI).

Table 3. Gastric tube cancer symptoms and methods of detection

Items	Gastrectomy (n = 30) Group A	EMR or ESD (n = 19) Group B
Symptom		
Passage disturbance	4	0
Palpation	4	0
Pain	4	0
Anemia	1	0
Occult blood	1	0
Weight loss	1	0
None	13	16
Unknown	3	3
Examination		
Endoscopy	17	16
Palpation	10	0
Barium meal	1	0
Unknown	2	3

EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

Time from esophagectomy to diagnosis of gastric tube cancer

The timing of diagnosis of gastric tube cancer varied from 1 to 30 years after esophagectomy (Figure 1). In Group A, gastric tube cancer was generally not detected for a long time after esophagectomy, whereas in Group B most cases were detected soon after esophagectomy. In our hospital, recurrence of esophageal cancer or gastric reflux soon after esophagectomy is an indication for an upper endoscopy at least once per year, which likely allowed for the detection of early-stage cancers in which EMR or ESD can be used. However, in the past, regular endoscopy was not performed from 6 years after esophagectomy, meaning the gastric tube cancer was often not detected until it was more advanced.

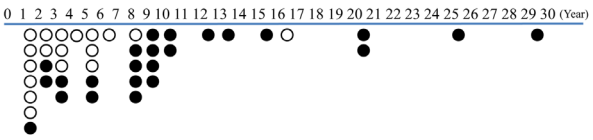

Figure 1. Time from esophagectomy to diagnosis of gastric tube cancer. ● Group A (gastrectomy), 6 patients were unknown; ○ Group B (endoscopic mucosal resection or endoscopic submucosal dissection) 1 patient was unknown.

Operative procedures undergone by patients in Group A

Table 4 shows the operative procedures undergone by the patients in Group A for gastrectomy and esophageal reconstruction. The antesternal route was used in 21 patients who underwent surgery from 1965 to 1992. The retrosternal route was used in 5 patients from 1985 to 2000. The posterior mediastinal route was used in 4 patients from 1986 to 2008. The antesternal route allows for a minimally invasive approach because we do not perform thoracotomy. A total of 12 patients underwent total gastrectomy and reconstruction with pedicled jejunum; however, one patient developed impaired blood flow in the jejunum and underwent additional venous reconstruction involving vascular anastomosis with the external jugular vein. In the remaining nine patients, the tumor mass was in the lower gastric tube; therefore, these patients underwent partial lower gastrectomy with preservation of the right gastroepiploic vessels. Of the five patients who underwent gastrectomy and reconstruction through the retrosternal route, two underwent total gastrectomy and reconstruction with pedicled jejunum, and two, due to their cancer being located primarily in the upper gastric tube, underwent upper gastric tube resection, vascular anastomosis of the internal thoracic artery and external jugular vein, and reconstruction with free jejunum. The remaining patient

Table 4. Operative procedures undergone by patients in Group A (gastrectomy)

Operative procedures	*n*
Antesternal route (*n* = 21)	
Total gastrectomy + reconstruction with pedicled jejunum	*n* = 11
Total gastrectomy + reconstruction with pedicled jejunum + revascularization with internal thoracic artery and external transvenous vein	*n* = 1
Partial lower gastrectomy + reconstruction with Roux-en-Y through laparotomy	*n* = 9
Retrosternal route (*n* = 5)	
Total gastrectomy through median sternotomy + reconstruction with pedicled jejunum	*n* = 2
Partial upper gastrectomy through median sternotomy + reconstruction with free jejunum	*n* = 2
Partial lower gastrectomy + reconstruction with Roux-en-Y through laparotomy	*n* = 1
Posterior mediastinal route (*n* = 4)	
Partial lower gastrectomy + reconstruction with Roux-en-Y through laparotomy	*n* = 2
Partial lower distal gastrectomy + reconstruction with Roux-en-Y through left thoracotomy	*n* = 2

underwent partial lower gastrectomy with preservation of the right gastroepiploic vessels.

Of the four patients who underwent gastrectomy and reconstruction through the posterior mediastinal route, one presented with a tumor in the middle gastric tube, and the remaining three presented with tumors in the lower gastric tube. For the cases of a large tumor in the middle and lower gastric tube, partial lower distal gastrectomy was performed through a left thoracotomy due to the resection reaching the superior margin of the tumor, with the right gastroepiploic vessels preserved. For the two patients for whom resection to the superior margin of the tumor in the lower gastric tube was possible through a laparotomy, partial lower gastrectomy through a laparotomy was performed with the right gastroepiploic vessels preserved.

Outcomes after surgery for gastric tube cancer

Two patients in Group A died within 30 days as a result of the gastrectomy (Table 5). Both patients underwent total gastrectomy and gastric tube reconstruction with a pedicled jejunum through the antesternal route. Recurrence of esophageal cancer was responsible for one death in Group A versus three deaths in Group B; for the three patients in Group B, although the gastric tube cancer was discovered shortly after esophagectomy and the patients went into remission following ESD, esophageal cancer later recurred and resulted in death. Ten patients who underwent gastrectomy for advanced gastric tube cancer died as a result of the gastric tube cancer, whereas none of the patients who underwent ESD and EMR did so. Both groups included two patients that died from other cancers, although their immediate cause of death was attributed to pneumonia.

Metachronous cancers after gastrectomy

Table 5. Outcomes after surgery for gastric tube cancer

Outcomes	Gastrectomy (*n* = 30) Group A	EMR or ESD (*n* = 19) Group B
Gastrectomy-related death (within 30 days)	2	0
Esophageal cancer–related death	1	3
Gastric tube cancer–related death	10	0
Death from other cancer	2	2
Death from other illness	2	1

EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

Table 6. Occurrence of metachronous cancers

Outcomes	Gastrectomy (*n* = 30) Group A	EMR or ESD (*n* = 19) Group B
Metachronous gastric tube cancer	0	4
Hypopharyngeal cancer	1	1
Gallbladder cancer	1	0
Cholangiocarcinoma	1	1
Colon cancer	1	1
Rectal cancer	1	0
Bladder cancer	1	1

EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

In Group B, four patients developed metachronous gastric tube cancers and in all four patients the cancer was treatable with EMR or ESD (Table 6). In addition, metachronous hypopharyngeal cancer, cholangiocarcinoma, colon cancer, and bladder cancer were observed in one patient each in both groups with two patients in each group dying of these cancers. The cause of death was a gallbladder cancer or a hypopharyngeal cancer in group A, a cholangiocarcinoma or a hypopharyngeal cancer in Group B.

Sites of metastasis after gastrectomy

Due to early detection of gastric tube cancer, no patients in Group B developed metastasis. In Group A, ten patients who underwent surgery for advanced gastric tube cancer developed metastasis (Table 7). Six patients developed dissemination after gastrectomy. Three patients who underwent total gastrectomy and reconstruction with a jejunal flap through the antesternal route developed axillary lymph node metastasis. Two of these patients subsequently died due to bone metastasis. One patient who underwent partial upper gastrostomy and free jejunal flap reconstruction through median sternotomy developed liver metastasis. He died 20 months later due to metastatic liver cancer.

Survival after gastrectomy

Five-year survival after gastrectomy was 38% in Group A and 60% in Group B (Figure 2). Median survival was

Table 7. Sites of metastasis after gastrectomy in the patients from Group A (gastrectomy) treated for advanced gastric tube cancer

Sites of metastasis	*n*
Right axillary lymph node metastasis	1
Left axillary lymph node metastasis	1
Bilateral axillary lymph node metastasis	1
Bone metastasis	2
Liver metastasis	1
Dissemination	6

938 days in Group A and 1,955 days in Group B. No significant difference between groups was observed (p = 0.1657); in Group B, although no patients died due to gastric tube cancer, some patients died from recurrence of esophageal cancer.

Follow-up for recurrence and metachronous cancers after esophagectomy at our hospital

Figure 3 shows the schedule of follow-up examinations after esophagectomy at our hospital. Testing to detect recurrence of esophageal cancer is performed until year 5. However, metachronous cancers can occur more than 5 years later. Therefore, although the number of CT and GS examinations will decrease, we must test to detect metachronous cancers for more than 10 years. Endoscopy by skilled doctors is performed taking into consideration oropharyngeal and hypopharyngeal cancer, which are difficult to detect metachronous cancers.

Discussion

Curative surgery for thoracic esophageal cancer is the most invasive of digestive tract surgeries, with the morbidity associated with esophagectomy in the range of 36.0% to 58.4% (*7,8*). Due to extremely poor outcomes in the past, cases of metachronous cancers after treatment for esophageal cancer were uncommon. However, the outcomes of esophagectomy for the treatment of esophageal cancer have been greatly improved through the introduction of extended lymphadenectomy and better perioperative management (*9,10*), and extended survival times means that the incidence of metachronous cancers after treatment for esophageal cancer is increasing.

The difficulty of treating advanced gastric tube cancer after esophagectomy depends on the route of reconstruction. Until 1990, the antesternal route was the standard route of gastric tube reconstruction. If the gastric tube is subcutaneous, this approach is relatively simple. However, with the retrosternal route and the posterior mediastinal route, the gastric tube must be approached through a median sternotomy and thoracotomy, respectively. This approach offers the advantages of good handling and visibility because of direct visualization of the gastric tube, but there is a

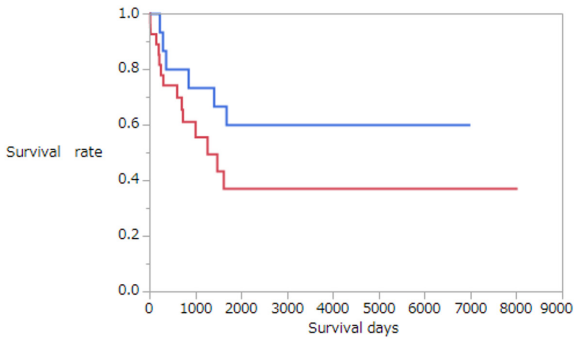

Figure 2. Survival rate after gastrectomy. p = 0.1657. Red: Group A (gastrectomy; n = 30) Blue: Group B (EMR or ESD; n = 19). EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

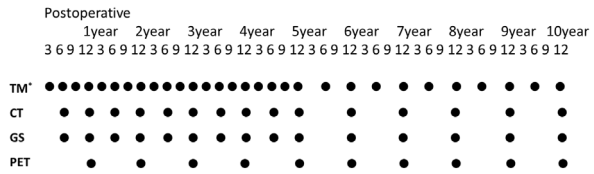

Figure 3. Follow-up examination schedule (years and months post-surgery) at our hospital. TM: tumor marker (CEA, SCC, CYFRA, P53), CT: computed tomography, GS: gastroscopy, PET: positron emission tomography.

higher risk of postoperative bleeding and osteomyelitis (*11*). In addition, postoperative pain often negatively effects respiration (*12*). With these reconstruction routes, total gastrectomy is extremely difficult, and complications occur frequently (*13,14*). For this reason, palliative resection, such as partial resection, is often performed (*15*).

In addition to gastric tube cancer resection, systematic lymphadenectomy must also be performed, as is common for typical gastric cancers. However, when a partial distal gastrectomy is performed, systematic dissection of lymph nodes at the greater curvature side of the gastric tube, which is fed by the right gastroepiploic vessels, is impossible. In such cases, station 6 lymph node dissection (*i.e.*, D1 dissection) is avoided. Consequently, in some cases, surgical treatment is abandoned in favor of chemotherapy and radiotherapy (*16,17*). Perfusion of the right gastroepiploic artery is commonly considered essential for blood supply to the gastric tube. Depending on the operative findings, it may be necessary to sacrifice this artery within the distal partial resection area of the gastric tube. In such cases, reconstruction of the artery *via* a vascular anastomosis should be considered. The extent of lymphadenectomy in cases of gastric tube cancer has not been standardized because long-term results of surgically treated gastric tube cancers are lacking. In our report, when the gastric tube was reconstructed through the antesternal route, we could perform total gastrectomy with lymph node dissection in 57% of cases and we could perform partial lower gastrectomy in 43% of cases.

We could perform an operation, which was minimally invasive surgery, without thoracotomy and reconstruction of the right gastroepiploic artery. In the five cases in which the retrosternal route was used, two cases involved total gastrectomy and reconstruction with a pedicled jejunum, two cases involved partial upper gastrectomy and reconstruction with a free jejunum, and one case involved partial lower gastrectomy and a Roux-en-Y anastomosis through laparotomy. We performed median sternotomy with risk of osteomyelitis in four patients to reach the gastric tube. Gastric tube cancers resectable through the posterior mediastinal route accounted for only four of the present cases, in which the lower gastric tube could be resected through a left thoracotomy or laparotomy. If the location of gastric tube cancer was high, we must perform invasive gastrectomy through a right thoracotomy. It will be a very invasive operation due to the adhesions of the previous operation.

Although the overall postoperative course of the present cases was good, and only two of the patients died as a result of the operation, there have been reports that the postoperative morbidity and mortality rates associated with gastrectomy are high (*18*). Both of the patients who died had undergone total gastrectomy and reconstruction with a pedicled jejunum for gastric tube cancer through the antesternal route and developed sepsis as a result of jejunal necrosis. If there was necrosis of pedicled jejunum, we should perform two step surgery. At first, we perform necrosectomy and external fistula construction. In the second stage surgery we perform reconstruction with a free jejunum. According to some reports (*19*), free jejunal transfer has a high success rate, but if vascular thrombosis occurs, the salvage of a failing flap with reanastomosis is difficult. The technique of vascular anastomosis has improved significantly in the last few years with the progress of breast cancer and transplantation (*20,21*). We could not find any literature regarding patterns of recurrence after gastrectomy. However, in the present study we observed three cases of axillary lymph node metastasis, a pattern of metastasis resembling breast cancer, after gastrectomy through the antesternal route.

In comparison to gastrectomy, EMR and ESD were found to be relatively safe procedures and did not result in any operation-related deaths. However, for these approaches, accurate diagnosis of cancer at an early stage is necessary and, depending on the site of gastric tube cancer, an experienced endoscopist is needed (*22-24*).

Survival outcomes after gastric tube treatment did not differ significantly between the gastrectomy group and the EMR or ESD group. The reason that the patients in Group B were caused by esophageal cancer-related death or death from other illness was because there were less terms from esophagectomy. In other words, it was because esophagectomy for esophageal cancer did not result in a complete cure. However, the present findings do show a marked difference in gastric tube cancer–related death between the two groups (Table 5). It was clear that ESD was beneficial to patients compared with gastrectomy with respect to the complexity of the procedure or gastrectomy-related death (Table 5). We must detect gastric tube cancer early in order to perform ESD or EMR without gastrectomy. Gastric tube cancer was detected within 5years after esophagectomy in 67% patients in the EMR or ESD group, suggesting that the patients who later die do so of recurrence or relapse of esophageal cancer. This indicates that early detection is the most important factor in gastric tube cancer (*25-27*).

At our hospital, with the understanding that the onset of gastric tube cancer varies from 1 to 30 years after esophagectomy, we now perform lifetime follow-up twice per year, even after five years have elapsed since esophagectomy. In addition, endoscopy is performed by an endoscopist who can accurately diagnose common sites of squamous epithelial cancers, such as tongue cancer and oropharyngeal or hypopharyngeal cancer.

This study has several limitations. First, this is a backward-looking observational study, and it is not a method that adds a high level of evidence as a means of drawing conclusions. Second, there were differences concerning the methods of reconstruction for esophagectomy depending on the background of the period. Third, due to the small sample size, the indicators shown in the tables were not statistically compared between the two groups.

Conclusion

In addition to recurrence and metastasis, gastric tube cancer is often observed after esophagectomy. The present findings highlight the importance of early detection of gastric tube cancer after esophagectomy and that the ESD and EMR procedures are safe and have significantly less complications compared with gastrectomy. Follow-up examinations should be scheduled with consideration given to the most frequent sites of gastric tube cancer occurrence and the time elapsed since esophagectomy.

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References

1. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol.

2014; 6:112-120.
2. Poon RT, Law SY, Chu KM, Branicki FJ, Wong J. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. Ann Thorac Surg. 1998; 65:1529-1534.
3. Kokawa A, Yamaguchi H, Tachimori Y, Kato H, Watanabe H, Nakanishi Y. Other primary cancers occurring after treatment of superficial oesophageal cancer. Br J Surg. 2001; 88:439-443.
4. Okamoto N, Ozawa S, Kitagawa Y, Shimizu Y, Kitajima M. Metachronous gastric carcinoma from a gastric tube after radical surgery for esophageal carcinoma. Ann Thorac Surg. 2004; 77:1189-1192.
5. Yamashita H, Kitayama J, Ishigami H, Yamaguchi H, Souma D, Nagano R, Nagawa H. Multiple gastric tube carcinomas after curative oesophagectomy. Dig Liver Dis. 2006; 38:214-215.
6. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013; 381:400-412.
7. Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K. Outcomes of extended radical esophagectomy for thoracic esophageal cancer. J Am Coll Surg. 1998; 186:306-312.
8. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002; 236:177-183.
9. Ide H, Nakamura T, Hayashi K, Endo T, Kobayashi A, Eguchi R, Hanyu F. Esophageal squamous cell carcinoma: pathology and prognosis. World J Surg. 1994; 18:321-330.
10. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg. 2000; 232:225-232.
11. Hosoya Y, Hirashima Y, Hyodo M, Haruta H, Kurashina K, Saito S, Zuiki T, Yasuda Y, Nagai H. A new operative technique for the resection of gastric tube cancer by means of lifting the anterior chest wall and videoscope-assisted surgery. Dis Esophagus. 2008; 21:275-278.
12. Tulla H, Takala J, Alhava E, Huttunen H, Kari A, Manninen H. Respiratory changes after open-heart surgery. Intensive Care Med. 1991; 17:365-369.
13. Sugiura T, Kato H, Tachimori Y, Igaki H, Yamaguchi H, Nakanishi Y. Second primary carcinoma in the gastric tube constructed as an esophageal substitute after esophagectomy. J Am Coll Surg. 2002; 194:578-583.
14. Ahn HS, Kim JW, Yoo MW, Park DJ, Lee HJ, Lee KU, Yang HK. Clinicopathological features and surgical outcomes of patients with remnant gastric cancer after a distal gastrectomy. Ann Surg Oncol. 2008; 15:1632-1639.
15. Shigemitsu K, Naomoto Y, Shirakawa Y, Haisa M, Gunduz M, Tanaka N. Five cases of early gastric cancer in the reconstructed gastric tube after radical resection for esophageal cancer. Jpn J Clin Oncol. 2002; 32:425-429.
16. Shiozaki A, Fujiwara H, Ichikawa D, Okamoto K, Komatsu S, Murayama Y, Ikoma H, Kuriu Y, Nakanishi M, Ochiai T, Kokuba Y, Sonoyama T, Otsuji E. Video-assisted surgery for gastric carcinoma arising in a gastric tube reconstructed retrosternally. Surg Today. 2012; 42:209-213.
17. Lee GD, Kim YH, Choi SH, Kim HR, Kim DK, Park SI. Gastric conduit cancer after oesophagectomy for oesophageal cancer: incidence and clinical implications. Eur J Cardiothorac Surg. 2014; 45:899-903.
18. Horie K, Oshikiri T, Kitamura Y, *et al.* Thoracoscopic retrosternal gastric conduit resection in the supine position for gastric tube cancer. Asian J Endosc Surg. 2020; 13:461-464.
19. Matsumine H, Kubo K, Hamahata A, Sakurai H. Deltopectoral and Pectoralis Musculocutaneous Flap Technique for Cervical Esophageal Reconstruction after Free-Jejunal-Flap Necrosis. Plast Reconstr Surg Glob Open. 2017; 5:e1444.
20. Kapila AK, Wakure A, Morgan M, Belgaumwala T, Ramakrishnan V. Characteristics and outcomes of primary interposition vascular grafts in free flap breast reconstruction. J Plast Reconstr Aesthet Surg. 2020; 73:2142-2149.
21. Nickel KJ, Staples J, Meeberg G, Kwan PO, Gilmour S, Bigam DL, Dajani K, Shapiro AMJ, Kneteman NM, Ladak A. The Transition to Microsurgical Technique for Hepatic Artery Reconstruction in Pediatric Liver Transplantation. Plast Reconstr Surg. 2021; 148:248e-257e.
22. Mukasa M, Takedatsu H, Matsuo K, Sumie H, Yoshida H, Hinosaka A, Watanabe Y, Tsuruta O, Torimura T. Clinical characteristics and management of gastric tube cancer with endoscopic submucosal dissection. World J Gastroenterol. 2015; 21:919-925.
23. Bamba T, Kosugi S, Takeuchi M, Kobayashi M, Kanda T, Matsuki A, Hatakeyama K. Surveillance and treatment for second primary cancer in the gastric tube after radical esophagectomy. Surg Endosc. 2010; 24:1310-1317.
24. Nonaka S, Oda I, Sato C, Abe S, Suzuki H, Yoshinaga S, Hokamura N, Igaki H, Tachimori Y, Taniguchi H, Kushima R, Saito Y. Endoscopic submucosal dissection for gastric tube cancer after esophagectomy. Gastrointest Endosc. 2014; 79:260-270.
25. Suzuki H, Kitamura M, Saito R, Motoyama S, Ogawa J. Cancer of the gastric tube reconstructed through the posterior mediastinal route after radical surgery for esophageal cancer. Jpn J Thorac Cardiovasc Surg. 2001; 49:466-469.
26. Kise Y, Kijima H, Shimada H, Tanaka H, Kenmochi T, Chino O, Tajima T, Makuuchi H. Gastric tube cancer after esophagectomy for esophageal squamous cell cancer and its relevance to Helicobacter pylori. Hepatogastroenterology. 2003; 50:408-411.
27. Shirakawa Y, Noma K, Maeda N, Ninomiya T, Tanabe S, Kikuchi S, Kuroda S, Nishizaki M, Kagawa S, Kawahara Y, Okada H, Fujiwara T. Clinical characteristics and management of gastric tube cancer after esophagectomy. Esophagus. 2018; 15:180-189.

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High-flow nasal cannula for severe COVID-19 patients in a Japanese single-center, retrospective, observational study: 1 year of clinical experience

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Abstract: High-flow nasal cannula (HFNC) can be effective in treating type 1 respiratory failure by reducing the severity of coronavirus disease 2019 (COVID-19). The purpose of this study was to assess the reduction of disease severity and safety of HFNC treatment in patients with severe COVID-19. We retrospectively observed 513 consecutive patients with COVID-19 admitted to our hospital from January 2020 to January 2021. We included patients with severe COVID-19 who received HFNC for their deteriorating respiratory status. HFNC success was defined as improvement in respiratory status after HFNC and transfer to conventional oxygen therapy, while HFNC failure was defined as transfer to non-invasive positive pressure ventilation or ventilator, or death after HFNC. Predictive factors associated with failure to prevent severe disease were identified. Thirty-eight patients received HFNC. Twenty-five (65.8%) patients were classified in the HFNC success group. In the univariate analysis, age, history of chronic kidney disease (CKD), non-respiratory sequential organ failure assessment (SOFA) ≥ 1, oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) before HFNC ≤ 169.2, were significant predictors of HFNC failure. Multivariate analysis revealed that SpO_2/FiO_2 value before HFNC ≤ 169.2 was an independent predictor of HFNC failure. No apparent nosocomial infection occurred during the study period. Appropriate use of HFNC for acute respiratory failure caused by COVID-19 can reduce the severity of severe disease without causing nosocomial infection. Age, history of CKD, non-respiratory SOFA before HFNC ≤ 1, and SpO_2/FiO_2 before HFNC ≤ 169.2 were associated with HFNC failure.

***Keywords*:** COVID-19, SARS-CoV-2, acute respiratory failure, high flow nasal cannula

Introduction

It has been more than 2 years since the start of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). While the pandemic is expected to be resolved as the vaccination rate increases, the emergence of highly infectious variant strains suggests that it will take some time for the pandemic to fully subside. To cope with the emergence of this novel coronavirus, socioeconomic activities must be restricted when necessary. However, lifting these restrictions leads to the spread of infection. This means that it is important to reduce disease severity in severe cases of COVID-19 to avoid excessive pressure on the healthcare system.

High-flow nasal cannula (HFNC) has been shown to be effective in treating type 1 respiratory failure and is expected to reduce disease severity in patients with COVID-19 (*1*). Even though HFNC was previously not recommended because of concerns about the risk of aerosol generation, a recent shift in opinion now considers HFNC treatment in the appropriate environment an effective method of choice. We previously published the treatment outcomes of HFNC administered between January and September 2020 and reported the possibility of a reduction of disease severity in severe COVID-19 cases, as well as increased safety (*2*). The purpose of this study was to expand the study period to 1 year and report the outcomes of HFNC treatment in patients with severe COVID-19 at our institution.

Patients and Methods

Study design and patients

From January 2020 to January 2021, we retrospectively

analyzed 513 consecutive patients with COVID-19 who were admitted to our hospital. We included patients with severe COVID-19 who received HFNC treatment owing to their worsening respiratory status in spite of conventional oxygen therapy. Disease severity was classified by National Institutes of Health criteria (*3*). HFNC success was defined as improvement in respiratory status and transfer to conventional oxygen therapy, while HFNC failure was defined as transfer to non-invasive positive pressure ventilation (NPPV) or ventilator, or death after treatment. Patients who died without intubation due to do-not-attempt-resuscitation (DNAR) orders were classified as HFNC failure. Patients who had HFNC attached for weaning either after extubation or withdrawal of NPPV were excluded.

Setting of HFNC

In our hospital's operation, HFNC was placed when the saturation of percutaneous oxygen (SpO_2) was below 93% even with nasal cannula or oxygen mask on oxygen flow rate of 6 L/min or more. The fraction of inspired oxygen (FiO_2) was determined by considering the oxygen delivery device and oxygen dosage prior to HFNC placement. The flow rate was adjusted in the range of 30-60 L/min depending on oxygenation and the patient's comfort level. The F&P 850 system (Fisher & Paykel Healthcare, Auckland, New Zealand) was used to provide HFNC therapy. The HFNC gas temperature was set at 31 °C (humidity: 32 mg/L) or 37 °C (humidity: 44 mg/L), depending on the patient's preference.

Environment during HFNC therapy

All patients who were administered HFNC used a private negative pressure room. Staff providing COVID-19 medical treatment underwent donning and doffing training of personal protective equipment beforehand. The medical care staff donned the personal protective equipment, including long-sleeved gowns, gloves, N95 masks, surgical masks with face shields, and hair caps, while attending to patients with HFNC as well as conventional oxygen therapy. There was no restriction on the frequency of entry into the HFNC treatment area. The patients were instructed to wear a surgical mask as much as possible during medical examination and care.

Data Collection

All data were retrospectively collected from electronic medical records. Recorded data included demographics (age, gender, body mass index), vital signs (body temperature, respiratory rate, heart rate, blood pressure, saturation of percutaneous oxygen), comorbidity, smoking status, detailed data related to HFNC use, and baseline treatment for COVID-19. The ratio of SpO_2/FiO_2 and the respiratory rate-oxygenation (ROX) index were collected as respiratory status before HFNC treatment. The ROX index was defined as the ratio of SpO_2/FiO_2 to respiratory rate. Glasgow Coma Scale, non-respiratory sequential organ failure assessment (SOFA), and quick SOFA (qSOFA) were also collected as assessment scores. The scores on admission day and before use of HFNC were calculated using the worst values observed within 6 hours after admission and 24 hours prior to HFNC treatment.

Statistical analyses

Descriptive statistics were used to summarize the baseline characteristics and to compare the success and failure rates of HFNC. Continuous variables were presented as medians (interquartile range), and binary variables were presented as numbers and frequencies (percentages). Continuous variables were compared using the Mann–Whitney *U*-test, and binary variables were compared using the Fisher's exact test. Vital signs and respiratory status before the attachment of HFNC and 2–6 hours after the attachment of HFNC were compared using Wilcoxon signed-rank test. To identify the predictors of HFNC failure, a univariate analysis was performed using baseline characteristics with $p < 0.2$. The receiver operating characteristic (ROC) curve analyses were performed to assess the cutoff values for the HFNC outcomes, which are the non-respiratory SOFA and SpO_2/FiO_2 before the attachment of HFNC. The area under the ROC curve (AUROC) was calculated as a measure of predictive capacity. A multivariate analysis was performed using logistic regression analysis, incorporating variables with $p < 0.05$ from the univariate analysis. Odds ratio (OR) were calculated along with 95% confidence interval (CI). A two-tailed *p*-value of < 0.05 was considered significant. All statistical analyses were performed using EZR (ver. 1.54; Jichi Medical University, Saitama, Japan).

Ethical approval

The National Center for Global Health and Medicine ethics review committee approved this study (NCGM-G-004024-00). The protocol for the research project conforms to the provisions of the Declaration of Helsinki for experiments involving humans.

Results

Thirty-eight patients received HFNC treatment due to worsening respiratory status. The median age was 66 years, and 30 patients (78.9%) were men. Baseline treatment consisted mostly of remdesivir, steroids, and heparin. Of the 38 patients who underwent HFNC therapy, 25 (65.8%) patients were subsequently transferred to conventional oxygen therapy and classified in the HFNC success group. However, the other 13

(34.2%) patients became critically ill (Figure 1). The median age of the patients in the HFNC success group was 59 years, which was significantly less than that of the patients in the HFNC failure group (74 years) (p = 0.008). Regarding comorbidities, the rate of chronic kidney disease (CKD) was significantly higher in the HFNC failure group (46.2% *vs*. 4%; p = 0.004). The median time from the onset of symptoms to the attachment of HFNC was 9 days in both groups. There were no differences in the body mass index, smoking history, or baseline treatment between the two groups. There was no difference in qSOFA before HFNC treatment between the two groups, while non-respiratory SOFA before HFNC use was significantly higher in the HFNC failure group (2 *vs*. 0, p = 0.0005). Regarding the vital signs and respiratory status before the attachment of HFNC, the SpO_2/FiO_2 was significantly lower in the HFNC failure group than in the HFNC success group (117.5 *vs.* 169.2, p = 0.01). The respiratory rate oxygenation (ROX) index also tended to be lower in the HFNC failure group (5.7 *vs.* 6.3, p = 0.28). In contrast, the heart rate (HR) and respiratory rate (RR) tended to be higher in the HFNC success group. Three (12%) patients in the HFNC success group and five (38.5%) patients in the HFNC failure group had DNAR orders (Table 1). Two to six hours after HFNC was attached, the RR worsened from 22 to 24.5 in the HFNC failure group (p = 0.62) but significantly improved from 24 to 22 in the HFNC success group (p = 0.009) (Figure 2A). Moreover, the HR changed from 87 to 85 in the HFNC failure group and significantly improved from 94 to 74 in the HFNC success group (p < 0.0001) (Figure 2B). Both groups showed improvement in the SpO_2/FiO_2 ratio, and the improvement in the HFNC success group from 169.2 to 192 was significant (p = 0.004) (Figure 2C). The ROX index rose slightly from 5.7 to 6.0 in the HFNC failure group (p = 0.3) and significantly improved from 6.3 to 9.5 in the HFNC success group (p = 0.0004) (Figure 2D).

Seven of the 13 patients in the HFNC failure group were directly placed on ventilators. Four patients were placed on NPPV after HFNC use, and two continued HFNC treatment until death (Table 1). The median durations of HFNC treatment in the HFNC success and failure groups were 5 days and 3.5 days, respectively, while the maximum FiO_2 was 60% and 100%, respectively. Eventually, seven patients (53.8%) in the HFNC failure group died, and four of those died without intubation following the DNAR order. As for the main cause of death, three patients had COVID-19-associated pneumoniae, two had acute respiratory distress syndrome due to secondary bacterial infection, one had acute kidney injury, and one had acute exacerbations of interstitial pneumoniae (Table 2).

Using the ROC curve, the best cutoff for non-respiratory SOFA was estimated to be 1.0 with a sensitivity of 0.92, specificity of 0.615, and AUROC of 0.815. The best cutoff of SpO_2/FiO_2 was 169.2 with a sensitivity of 0.520, specificity of 0.923, and AUROC of 0.758. In the univariate analysis, age (OR = 1.08; 95% CI: 1.02–1.15; p = 0.012), history of CKD (OR = 20.6; 95% CI: 2.11–201.0; p = 0.009), non-respiratory SOFA before HFNC ≥ 1 (OR = 10.6; 95% CI: 2.17–51.4; p

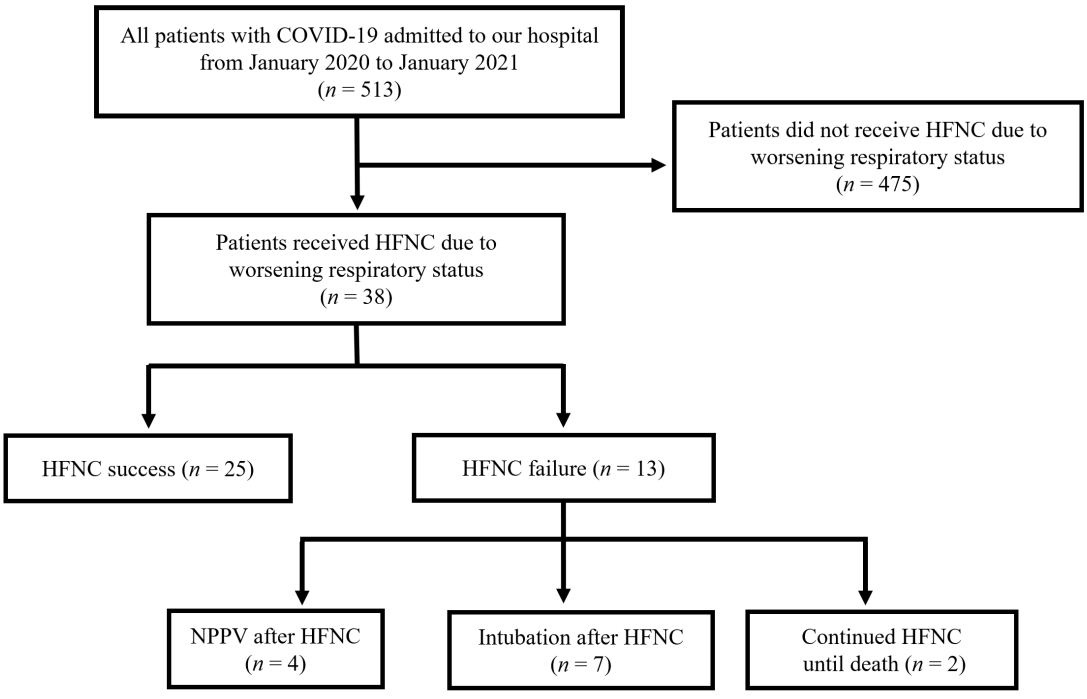

Figure 1. Flow diagram and clinical outcome of patients. COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation.

Table 1. Baseline characteristics of patients who were administered HFNC therapy due to deterioration

Variables	Total (*n* = 38)	HFNC success (*n* = 25)	HFNC failure (*n* = 13)	*p*
Age (years), median (IQR)	66 (51-75)	59 (50-70)	74 (68-82)	0.008
Gender (Male), *n* (%)	30 (78.9%)	22 (88%)	8 (61.5%)	0.094
Body mass index (kg/m^2), median (IQR)	26.8 (22.6-30.2)	26.6 (24.2-30.6)	27.2 (22.3-28.8)	0.43
Comorbidity				
Hypertension	23 (60.5%)	13 (52%)	10 (76.9%)	0.18
Diabetes mellitus	19 (50%)	12 (48%)	7 (53.8%)	1
Dyslipidemia	11 (28.9%)	6 (24%)	5 (38.5%)	0.46
Asthma	3 (7.9%)	3 (12%)	0	0.54
Coronary heart disease	3 (7.9%)	2 (8%)	1 (7.7%)	1
Chronic kidney disease	7 (18.4%)	1 (4%)	6 (46.2%)	0.004
Immunosuppression	1 (2.6%)	0	1 (7.7%)	0.34
Smoking status				
Never smoker	14 (36.8%)	11 (44%)	3 (23.1%)	0.29
Current or former smoker	24 (63.2%)	14 (56%)	10 (76.9%)	0.29
Baseline treatment				
Remdesivir, *n* (%)	31 (81.2%)	22 (88%)	9 (69.2%)	0.20
Hydroxychloroquine, *n* (%)	3 (7.9%)	1 (4%)	2 (15.4%)	0.27
Favipiravir, *n* (%)	8 (21%)	7 (28%)	1 (7.7%)	0.22
Tocilizumab, *n* (%)	2 (5.3%)	1 (4%)	1 (7.7%)	1
Lopinavir-ritonavir, *n* (%)	1 (2.6%)	0	1 (7.7%)	0.34
Steroid, *n* (%)	37 (97.4%)	25 (100%)	12 (92.3%)	0.34
Heparin, *n* (%)	32 (84.2%)	23 (92%)	9 (69.2%)	0.15
PMX-DHP, *n* (%)	7 (18.4%)	5 (20%)	2 (15.4%)	1
Convalescent plasma therapy, *n* (%)	3 (7.9%)	2 (8%)	1 (7.7%)	1
Implementation of HFNC				
Days after onset (days), median (IQR)	9 (7-11.8)	9 (8-12)	9 (6-11)	0.66
Days after admission (days), median (IQR)	2 (1-2)	2 (1-2)	2 (1-3)	0.50
Severity score before HFNC, median (IQR)				
Glasgow Coma Scale, median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	NA
qSOFA, median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.81
non-respiratory SOFA, median (IQR)	0 (0-1.75)	0 (0-0)	2 (1-3)	0.0005
Vital signs and respiratory status before HFNC				
Systolic blood pressure (mmHg), median (IQR)	115.5 (105.3-124.8)	118 (107-127)	109 (100-117)	0.093
HR (bpm), median (IQR)	93 (82.3-102.5)	94 (91-95)	87 (83-100)	0.83
RR (/min), median (IQR)	24 (20.5-28)	24 (22-28)	22 (20-24)	0.14
SpO_2/ FiO_2, median (IQR)	154.2 (108.5-176)	169.2 (132.9-184.6)	117.5 (103.3-153.3)	0.01
ROX index, median (IQR)	6.3 (5.1-7.5)	6.3 (5.1-7.7)	5.7 (5.0-6.9)	0.28
DNAR, *n* (%)	8 (21.1%)	3 (12%)	5 (38.5%)	0.094

HFNC, high-flow nasal cannula; IQR, interquartile range; qSOFA, quick sequential organ failure assessment; PMX-DHP, polymyxin-B direct hemoperfusion; HR, heart rate; RR, respiratory rate; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen, ROX index; respiratory rate-oxygenation index; DNAR, do-not-attempt-resuscitation.

= 0.004), and SpO_2/FiO_2 before HFNC ≤ 169.2 (OR = 13.0; 95% CI: 1.46–116.0; p = 0.021) were found to be statistically significant predictors of HFNC failure. We performed a multivariate analysis and calculated the adjusted ORs by incorporating variables with $p < 0.05$. Multivariate analysis revealed that an SpO_2/FiO_2 ratio ≦ 169.2 (adjusted OR = 15.9, 95% CI: 1.07–236.0, p = 0.004) before HFNC treatment was an independent predictor of HFNC failure (Table 3).

The medical staff treating patients with COVID-19, with or without HFNC, implemented airborne and contact infection control measures, including the use of N95 masks. No restrictions were placed on the frequency of entry into the HFNC treatment area. When HFNC apparatuses were attached, all patients were managed in negative-pressure individual rooms to prevent nosocomial infection resulting from aerosol production. No apparent nosocomial infection occurred during the study period.

Discussion

The risk of nosocomial infection poses a concern when the aerosol-generating device, HFNC, is applied to patients with COVID-19. However, our retrospective study showed that with a conducive environment, appropriate equipment, proper procedure, and infection control measures, it was possible to prevent 65.8% of severely ill patients from further deterioration of their condition without causing obvious nosocomial infections of COVID-19.

Previous studies have shown that HFNC treatment results in a lower intubation rate than noninvasive ventilation and standard oxygen therapy in patients with acute respiratory failure (*1*). HFNC has also been shown to be effective for managing acute respiratory failure caused by COVID-19 for the following reasons. Two phenotypes of COVID-19 pneumonia have been identified (*4*). As the disease progresses from Type L to

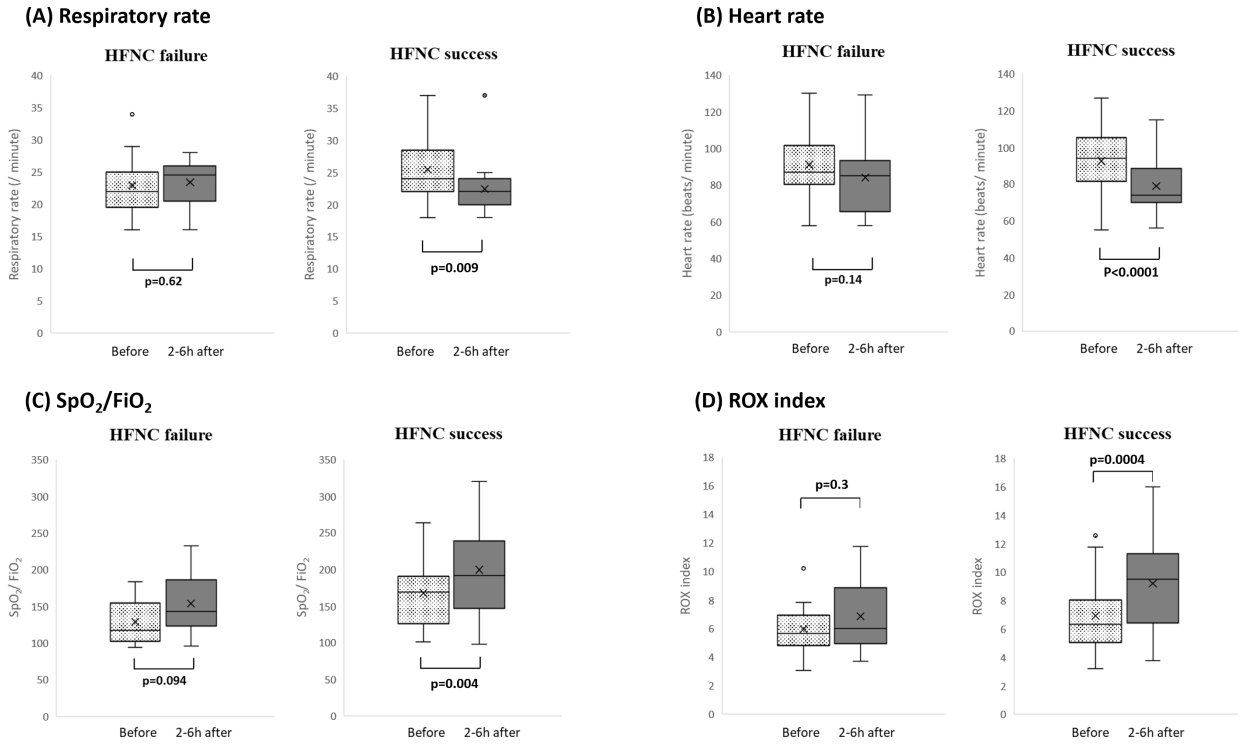

Figure 2. Sequential change of vital signs and respiratory status two to six hours after high-flow nasal cannula (HFNC) therapy. (A) The respiratory rate worsened from 22 (20-24) to 24.5 (21.5-26) in the HFNC failure group ($p = 0.62$) and improved from 24 (22-28) to 22 (20-24) in the HFNC success group ($p = 0.009$). **(B)** The heart rate changed from 87 (83-100) to 85 (71-93) in the HFNC failure group ($p = 0.14$) and improved from 94 (82-105) to 74 (70-86) in the HFNC success group ($p < 0.0001$). **(C)** The oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) changed from 117.5 (103.3-153.3) to 143.1 (124-184) in the HFNC failure group ($p = 0.094$) and improved from 169.2 (132.9-184.6) to 192 (155-237.5) in the HFNC success group ($p = 0.004$). **(D)** The respiratory rate-oxygenation index (ROX) index slightly rose from 5.7 (5.0-6.9) to 6.0 (5.3-8.0) in the HFNC failure group ($p = 0.3$) and improved from 6.3 (5.1-7.7) to 9.5 (6.6-11.3) in the HFNC success group ($p = 0.0004$). All data are presented as medians (interquartile range). HFNC, high-flow nasal cannula; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen, ROX index; respiratory rate-oxygenation index.

Table 2. Treatment details and clinical outcome of HFNC therapy

Variables	HFNC success ($n = 25$)	HFNC failure ($n = 13$)
Duration of HFNC (days), median (IQR)	5 (3-6)	3.5 (2-7.3)
Time to NPPV or intubation from HFNC		
< 24/ < 48/ < 72/ ≥ 72 (hours), *n*	NA	5/ 1/ 3/ 2
Setting of HFNC		
Maximum flow rates (L/min), median (IQR)	50 (40-50)	60 (50-60)
Maximum FiO_2 (%), median (IQR)	60 (50-75)	100 (100-100)
Death, *n* (%)	0	7 (53.8%)
DNAR, *n*	NA	4
The main cause of death		
COVID-19 pneumoniae	NA	3
ARDS due to secondary bacterial infection	NA	2
Acute kidney injury	NA	1
Acute exacerbation of interstitial pneumonia	NA	1

HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation; IQR, interquartile range; FiO_2, fraction of inspired oxygen; DNAR, do-not-attempt-resuscitation; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome.

Type H, respiratory distress increases due to decreased lung compliance, increased dead space, increased atelectasis, carbon dioxide retention, fatigue, and anxiety. At that point, the respiratory center is stimulated through various chemoreceptors and mechanoreceptors in the respiratory physiology, causing a strong respiratory drive (*5*). Strong spontaneous breathing increases transpulmonary pressure and causes patient self-inflicted lung injury (*6.*).

In addition to disease severity and intravascular microthrombosis, self-inflicted lung injury is also known to be closely related to COVID-19 pneumonia. Therefore, HFNC can be used to target the positive end-expiratory pressure-like effect, improvement of oxygenation, and washout effect of CO_2. Although pain and emotional stimuli from the hypothalamus also transmit stimuli to the respiratory center, HFNC is superior to NPPV in terms of comfort (*1*). In the present study, HFNC was attached to all patients as there was no problem associated with the tolerability. Other advantages of HFNC include facilitation of eating, drinking, talking, oral care, rehabilitation, and performing awake self-proning.

There have been several reports on HFNC treatment

Table 3. Multivariate logistic regression analysis for the predictors of HFNC failure

Variables	Univariate Odds ratio (95% CI)	*p* value	Multivariate Odds ratio (95% CI)	*p* value
Age	1.08 (1.02-.)	0.012	1.06 (0.98-1.15)	0.13
Gender, male	0.22 (0.04-1.13)	0.07		
CKD, presence	20.6 (2.11-201.0)	0.009	8.25 (0.55-124.0)	0.13
Hypertension, presence	3.08 (0.68-13.9)	0.15		
Non-respiratory SOFA before HFNC <1	Ref.			
≥ 1	10.6 (2.17-51.4)	0.004	3.89 (0.48-31.7)	0.2
Systolic blood pressure before HFNC	0.97 (0.92-1.02)	0.18		
RR before HFNC	0.89 (0.76-1.04)	0.15		
SpO_2/ FiO_2 ratio before HFNC >169.2	Ref.			
≤ 169.2	13.0 (1.46-116.0)	0.021	15.9 (1.07-236.0)	0.004

HFNC, high-flow nasal cannula; CI, Confidence interval; CKD, Chronic kidney disease; SOFA, sequential organ failure assessment; RR, respiratory rate; SpO_2, saturation of percutaneous oxygen; FiO_2, fraction of inspired oxygen; ROX index; respiratory rate-oxygenation index; Ref, Reference.

for patients with COVID-19 in clinical practice. A significant lower rate of ventilator placement on day 28 was reported in the patients who received HFNC than the patients who did not at four sites in Paris, France (56% *vs.* 75%, $p < 0.001$) (*7*). A report from Temple University in the United States showed a 67% intubation avoidance rate in the HFNC group of patients with moderate-to-severe hypoxemic respiratory failure, which is very similar to the data reported in this study (*8*).

In this study, we used the SpO_2/FiO_2 ratio to evaluate the results because this was not a prospective observational study. The timing of arterial blood gas collection was determined by individual clinicians, and there were many missing data. According to Rice *et al.*, the SpO_2/FiO_2 ratio threshold of 235 identified PaO_2/FiO_2 ratio ≤ 200 with a sensitivity of 85% and a specificity of 85% (*9*). The baseline SpO_2/FiO_2 ratio for the entire study was 154.2, which is considered less than PaO_2/FiO_2 ratio of 200 and is relatively close to the value reported by Patel *et al*. (*8*). In this study, the baseline ROX index before HFNC was 6.3, which was higher than that reported by Richard Mellado-Artigas *et al.* (*10*). Since our previous report considered that early introduction of HFNC could lead to prevention of patient self-inflicted lung injury, it is possible that the current study may have resulted in an earlier introduction of HFNC than other reports (*2*). In the early stages of acute respiratory failure due to COVID-19, respiratory center drive may not occur, and the RR – the denominator of the ROX index – may not increase because lung compliance is not decreased (*5*).

Regarding predictors of HFNC failure, a prospective multicenter cohort study in Spain, involving patients with acute respiratory failure admitted to the intensive care unit, reported that non-respiratory SOFA and ROX indices were the main predictors of intubation in the multivariate analysis (*10*). According to a report by Patel *et al.,* SpO_2/FiO_2 ratio (<100) and history of CKD were predictors of HFNC failure (*8*). Consistent with their findings, the univariate analysis of the present study showed that a history of CKD and SpO_2/FiO_2 (≤ 169.2) were statistically significant predictors of HFNC failure. A possible explanation for the failure of the ROX index before HFNC treatment to be a predictor of HFNC failure in the present study might be the influence of the lower RR values in the HFNC failure group. This might have occurred because of "silent or happy hypoxia", which can lead to rapid clinical deterioration in patients with COVID-19 (*5*). Two to six hours after HFNC was attached, the RR worsened in the HFNC failure group but significantly improved in the HFNC success group. Thus, it may be important to monitor changes in the RR in patients receiving HFNC therapy.

Regarding the safety of HFNC for patients with COVID-19, the risk of nosocomial infection cannot be completely eliminated because HFNC is classified as a type of aerosol-generating procedure similar to NPPV. While our initial approach toward the use of HFNC treatment was cautious, with greater accumulation of data clarifying its efficacy and safety in patients with COVID-19, guidelines in various countries have begun to accept the use of HFNC treatment provided that infection control measures are thoroughly implemented in an appropriate environment. Among these, HFNC has been considered superior to conventional oxygen therapy and NPPV in the Surviving Sepsis Campaign Guideline (*11*). The results of the simulation also showed that the droplet diffusion distance was shorter with HFNC compared to reservoir masks and Venturi masks (*12*). However, there are reports of simulation results showing that the aerosol diffusion distance increases when the HFNC is loosely attached at a flow of 60 L/min. Therefore, the appropriate use of the HFNC is critical (*13*). As a result of the appropriate use and proper environmental measures, no apparent nosocomial infection occurred in our facility throughout the study period.

This study has several limitations. First, this study was retrospective, and the treatment setting was not unified. Variability in vital signs and respiratory parameters can occur before initiating HFNC because

there is no standard protocol for initiating HFNC treatment. Remdesivir, steroids, and heparin were administered in most patients; however, the type and amount of steroids varied according to the clinical physician's discretion, which can be a confounding factor. Furthermore, we had to substitute SpO_2/FiO_2 for PaO_2/FiO_2 ratio because the arterial blood gas analysis was not performed with appropriate timing. A unified protocol for HFNC use and medical treatment is necessary, and arterial blood gas analysis should be appropriately performed. Second, a prediction model for HFNC failure was not derived because the number of cases that received HFNC treatment were too few to prepare a validation dataset.

In conclusion, the appropriate use of HFNC treatment for COVID-19 patients with acute respiratory failure can reduce the severity of disease in severe patients without causing nosocomial infections. Age, prior history of CKD, non-respiratory SOFA before HFNC ≥ 1, and SpO_2/FiO_2 before HFNC ≤ 169.2 were predictive variables associated with HFNC failure. In the future, it will be necessary to assess the validity of the prediction variables for HFNC outcomes in a large-scale group study. Moreover, further accumulation of data on COVID-19 and other emerging infectious diseases are necessary.

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References

1. Frat JP, Thille AW, Mercat A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015; 372:2185-2196.
2. Katsuno T, Suzuki M, Hojo M, Terada J, Nakamura K, Suzuki T, Miyazato Y, Sugiyama H. Clinical experience with high-flow nasal cannulas for coronavirus disease 2019 patients in Japan. Respir Investig. 2021; 59:569-572.
3. National Institutes of Health. COVID-19 treatment guidelines – clinical spectrum of SARS-CoV-2 infection. *https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum* (accessed December 27, 2022).
4. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020; 46:1099-1102.
5. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020; 21:198.
6. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med. 2017; 195:438-442.
7. Demoule A, Vieillard Baron A, Darmon M, Beurton A, Géri G, Voiriot G, Dupont T, Zafrani L, Girodias L, Labbé V, Dres M, Fartoukh M, Azoulay E. High-flow nasal cannula in critically III patients with severe COVID-19. Am J Respir Crit Care Med. 2020; 202:1039-1042.
8. Patel M, Gangemi A, Marron R, *et al.* Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. BMJ Open Respir Res. 2020; 7:e000650.
9. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO_2/FIO_2 ratio and the PaO_2/FIO_2 ratio in patients with acute lung injury or ARDS. Chest. 2007; 132:410-417.
10. Mellado-Artigas R, Mujica LE, Ruiz ML, Ferreyro BL, Angriman F, Arruti E, Torres A, Barbeta E, Villar J, Ferrando C; COVID-19 Spanish ICU Network. Predictors of failure with high-flow nasal oxygen therapy in COVID-19 patients with acute respiratory failure: a multicenter observational study. J Intensive Care. 2021; 9:23.
11. Alhazzani W, Møller MH, Arabi YM, *et al.* Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020; 46:854-887.
12. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J. 2020; 55:2000892.
13. Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, Gin T, Chan MTV. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP *via* different masks. Eur Respir J. 2019; 53:1802339.

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Distress and impacts on daily life from appearance changes due to cancer treatment: A survey of 1,034 patients in Japan

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Abstract: This study aimed to clarify the psychosocial difficulties and impacts that cancer patients face from appearance changes, in order to develop a patient support program. An online survey was administered to patients registered with an online survey company who met the eligibility criteria. The study population was randomly selected from gender and cancer types to create a sample that reflected the proportion of cancer incidence rates in Japan as much as possible. Out of a total of 1034 respondents, 601patients (58.1%) experienced appearance change. Symptoms that were reported to have a high distress level and prevalence rate, and that widely required provision of information were such as alopecia (22.2%), edema (19.8%) and eczema (17.8%). Distress levels and personal assistance requirements were high particularly for patients who experienced stoma placement and mastectomy. More than 40% of patients who experienced appearance change had quit or were absent from work or school, and reported that their social activities were negatively affected by the visually notable changes in their appearance. Concerns about "receiving pity from others" or about "the exposure of cancer" due to their appearance change also led patients to reduce outings ($\beta = 0.32$ and $\beta = 0.31$ respectively, $p < 0.001$) and social interactions with others ($\beta = 0.34$ and $\beta = 0.36$ respectively, $p < 0.001$) and increased the discord in human relationships ($\beta = 0.21$ and $\beta = 0.19$ respectively, $p < 0.001$). Results from this study indicate the areas in which more support is required from healthcare professionals, as well as the need for interventions for patient cognition to avoid maladaptive behaviors in cancer patients who experience appearance changes.

***Keywords*:** appearance change, alopecia/hair loss, coping behavior, quality of life, appearance care

Introduction

The number of cancer patients is on the rise (*1*). The top five most common types of cancer in Japan (2019) are colorectal cancer (155,625) lung cancer (126,548) stomach cancer (124,319) breast cancer (97,812) and prostate cancer (94,749) (*2*). But long-term survival is possible for some types of cancer (*3*). At the same time, in Japan, duration of hospital stays was 17.1 days (2017), a reduction of one-third from 20 years prior (*4*), and outpatients account for 41-68% of people receiving chemotherapy (*5*). As these numbers indicate, contemporary cancer patients live and interact with society while undergoing treatment. However, such social interactions also become an opportunity for patients to be highly aware and sensitive towards appearance changes due to cancer treatments such as surgeries, radiation, and chemotherapy. This may result in hesitation towards treatment as well as decreased quality of life. Therefore, it is necessary for medical professionals to provide appropriate support to patients regarding their appearance concerns.

Previous studies have reported that 84.9% of male patients experience appearance change from cancer treatment (*6*), and that 80.3% of patients in outpatient chemotherapy centers are concerned about physical changes in various parts of their body (*7*). The most prevalent topic of study is hair loss (*8*), as it decreases body image and level of psychosocial happiness, and carries a high likelihood for depression (*9*). It has also been identified that patients have difficult experiences because of negative reactions from others that noticed their change in appearance (*10,11*), and they spend a lot of energy concealing their symptoms (*12,13*) because they are concerned about being treated differently by others and because some appearance changes are a physical indication of cancer (*14,15*).

However, Previous studies have been conducted at specialized cancer hospitals in urban areas (*6*) or outpatient treatments centers (*7*), and the results are specific to the study region or department, or are limited to breast cancer (*9-11,14*) or male patients (*6*). The last study on all cancer types was conducted in 2009 (*7*), making the results outdated by over 10 years. There is a

lack of recent studies to understand the current realities of appearance change in cancer patients. Therefore, this study was conducted with a sample that reflects the actual proportions of cancer incidence rates by gender and site as much possible.

This study has the following two purposes: *i*) To obtain a clear understanding of the appearance changes that cancer patients experience due to treatment, and their respective distress levels, to examine the symptoms that require prioritized support and care; and *ii*) To obtain a clear understanding of the psychosocial difficulties and the related factors that patients face, such as the impact on their daily lives, to identify the essential perspective for when healthcare professionals should support patients. Based on the above, this study examined the hypothesis that patient concerns about changes in physical appearance directly lead to behavioral inhibition in daily life.

We conducted this study to obtain foundational data for the development of a patient support program. This article reports the data gathered as part of this project, which indicate the psychosocial difficulties patients face as a result of changes in physical appearance from cancer treatment.

Methods

Participants

More than 1,000 male and female patients between the ages of 20 and 75 who were either currently undergoing cancer treatment or under post-treatment observation were included. All participants agreed to participate and had the technical abilities to respond to the online surveys.

Procedure

Anonymous self-administered surveys were provided online to conduct a cross-sectional study. First, the researchers investigated Internet-based research companies that are members of the Japan Marketing Research Association (JMA) with the aim of minimizing significant bias in the registered attributes and the frequency of updating the registered information by referring to publicly available information. This resulted in Macromill, Inc. being selected to conduct the survey. Next, we conducted a screening survey of the monitors who had registered to participate in surveys with the Internet survey company and selected eligible patients.

Then, we randomly selected candidates for the survey in proportion to the incidence rate of cancer by sex and site (17), and conducted an Internet survey until more than 1000 valid responses were obtained. In the Japanese estimates of cancer incidence by site (2017), the stomach was the most common site for males, followed by the lung, prostate, colon/rectum, and liver. The most common cancer site for females was the breast, followed by the colon/rectum, stomach, lung, and uterus. In addition, ages (20s, 30s, 40s, 50s, and 60s or older) were also automatically allocated so that differences in attitudes by age could be examined.

This study was approved by the Research Ethics Review Committee of the National Cancer Research Centre (File No. 2017-417) and was conducted from March 2, 2018 to March 22, 2018.

Measures

The survey collected information on patient demographics, appearance change and the associated distress level from cancer treatment, and impacts on daily and social life. Survey items and questions were developed based on preexisting studies (*5,6*) and preliminary research by a team of one doctor, two nurses, two clinical psychologists, two cosmetic and makeup specialists, and four patient representatives.

For patient demographics, participants were asked to identify their age, gender, occupation, highest level of education, and the type of cancer for which they are undergoing, or have undergone treatment.

For appearance change due to treatment and related distress participants were first asked if they experienced any appearance changes due to treatment. Those who answered yes were then asked if they (a) were currently experiencing, (b) had experienced in the past, or (c) had never experienced, each item of appearance change on the survey (29 questions). Finally, those who were experiencing or had experienced an item scored 0 to 3 were asked to identify their distress level when the experience was most severe. 0 points indicated that they experienced appearance change but no distress, 1 point indicated a low level of distress (indicated a bit of distress), 2 points indicated a medium level of distress (indicated distress), and 3 points indicated a high level of distress (indicated severe distress). The method of scoring the distress level was based on previous studies (*6*).

Regarding the impacts of appearance changes on daily and social life, 12 experiences related to how the appearance changes impact daily life and social relationships were listed. Participants were asked to answer if they (1) experienced the impact, (2) experienced the impact to an extent, (3) not applicable, (4) did not really experience the impact, or (5) did not experience the impact at all.

Furthermore, the specifics of this patient's coping behaviors and information and support needs are presented in a separate paper (*16*). As patients' coping behaviors, we investigated information gathering behavior and daily grooming behavior. In order to clarify the actual situation of information collection on appearance changes, we asked the participants whether they obtain information from medical professionals and their satisfaction level, and whether they use 20 sources

of information on appearance changes (family members, patient groups, product retailers, Internet information, *etc.*) and their trust level. Satisfaction and trust were rated on a 4-point scale ranging from "very much so" (4 points) to "not at all" (1 point). They were also asked about 24 daily grooming behaviors (wigs, moisturizers, *etc.*) and their costs (purchase price of wigs, *etc.*).

Descriptive statistics were calculated from participants' sociodemographic statistical variables and their experiences of appearance change. To determine the most highly distressing experiences, the average level of distress was calculated for each physical change. A chi-square test was conducted on the data collected on the impacts on daily and social life in order to examine the difference between genders or ages. A covariance structured analysis was also conducted to examine how patient concerns about changes in appearance affect behavioral inhibition. Statistical analyses were conducted using IBM® SPSS® Amos 16.0. The multiplicity of the tests was not adjusted for because this was an exploratory study.

Results

Participant demographics

By the registration deadline, a total of 1,034 participants, 518 men and 516 women, attended (Table 1). The average age was 58.7 ± 10.6 years with a median age of 60 (26-74) years. The most common cancer types were stomach for men 93 (9.0%) and breast for women 120 (11.6%). The top cancer types in both sexes were the top 5 most common cancers in Japan. Most participants were working, with 347 (33.6%) working full-time and 505 (48.8%) working part-time. The most common final education was a university or graduate degree, 426 (41.2%).

Table 1. Attributes of the study population

Characteristics	*n* (%), *n* = 1034
Gender	
Male	518 (50.0)
Female	516 (50.0)
Type of Cancer	
Stomach	93 (9.0)
Men	
Large Intestine	80 (7.7)
Lung	79 (7.6)
Prostate	76 (7.4)
Liver	29 (2.8)
Others	161 (15.6)
Women	
Breast	120 (11.6)
Large Intestine	82 (7.9)
Stomach	59 (5.7)
Lung	36 (3.5)
Uterine	36 (3.5)
Others	183 (17.7)
Age	
20-29	3 (0.3)
30-39	50 (4.8)
40-49	170 (16.5)
50-59	266 (25.7)
60-74	545 (52.7)
Occupation	
Full-time	347 (33.6)
Part-time	505 (48.8)
Unemployed (housewife included)	127 (12.3)
Others	55 (5.3)
Highest level of Education	
Middle School	34 (3.3)
High School	325 (31.4)
Vocational School	103 (10.1)
College degree	146 (14.1)
Bachelor / Master's degree	426 (41.2)
Others	0 (0.0)

Changes in physical appearance from treatment

Prevalence of appearance change and respective symptoms

A total of 601 patients (58.1%) reported that they experienced appearance change. There were participants who experienced a change in appearance in all 27 items, but the most commonly experienced change was surgical therapy-induced scars on the body surface (49.1%). Other symptoms that were reported by more than 15% of all participants were hair loss (22.2%), change in body from weight loss (22.1%), weak and thin nails (21.2%), dry skin (20.9%), sensitive skin (19.8%), edema on the face and body (including lymphoedema) (19.8%), discoloration of the nails (*e.g.* white lines, hyper pigmentation) (19.6%), injection site scars on arms (19.0%), discoloration of the skin (hyperpigmentation) (18.0%), dermatitis (17.8%), loss of body hair (arms, legs, nose, and pubic) (17.1%), and blemishes (15.1%). It was speculated that most of the changes were due to chemotherapy.

Distress level for each appearance change

Distress level of each symptom experienced for 29 appearance symptoms is shown in Figure 1 and Figure 2. To clarify the frequency of occurrence and distress level, we divided the symptoms into two groups: those with a relatively large number of participants who experienced them (100 or more: Figure 1) and those with a small number of people who experienced them (less than 100: Figure 2). The mean distress level for all 29 symptoms was 1.34 (± 0.45) points.

The number of participants who experienced symptoms was high, and the distress level for each symptom was higher than average for hair loss, change in body shape from weight gain, edema on the face and body (including lymphoedema), loss of eye lashes, dermatitis and skin sensitivity.

As for the symptoms that were experienced by a small number of participants, they had notably high distress levels (1.79 points or higher, which is over 1 standard deviation of the overall average). These include

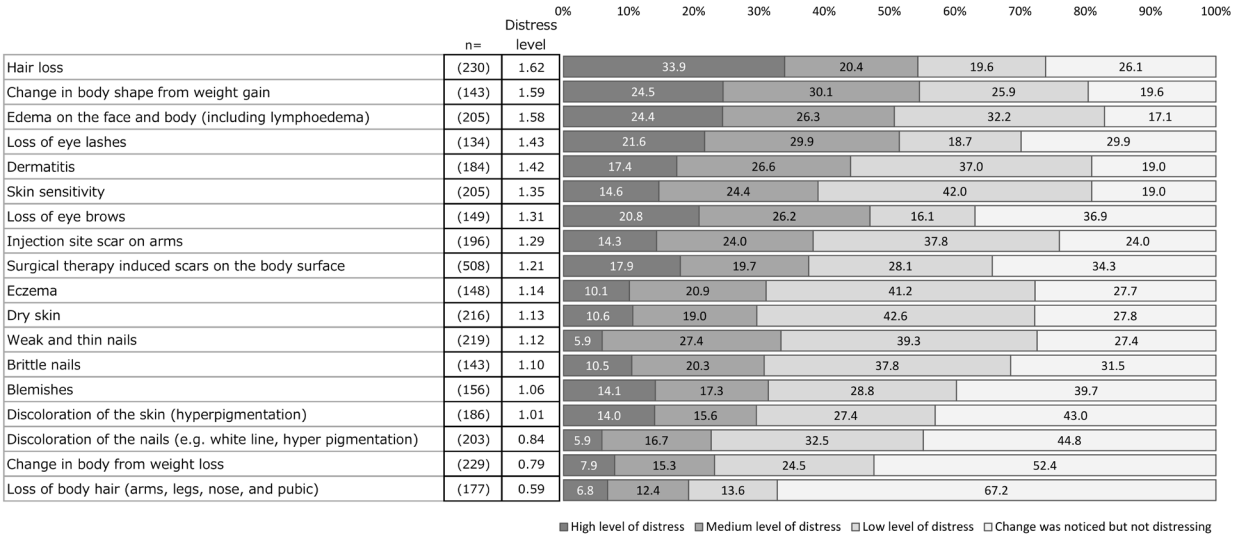

Figure 1. Distress level of symptoms experienced by 100 people or more.

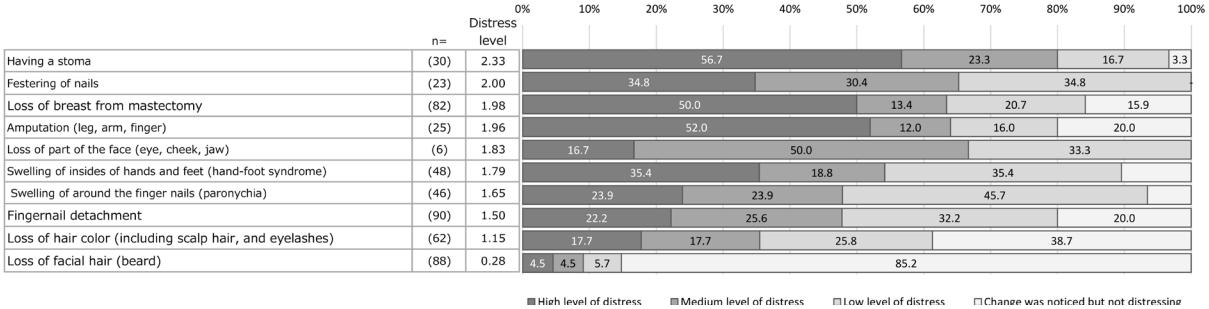

Figure 2. Distress level of symptoms experienced by less than 100 people.

stoma, festering of nails, loss of breast from mastectomy, amputation, loss of part of the face and hand-foot syndrome.

For breast cancer patients only, distress level for hair loss (2.16 points) was higher than loss of breast from mastectomy (2.00 points).

Impact on daily life

Participants were asked 12 survey items related to how appearance change impacted their thoughts and activities in daily life. Participants who indicated that they "experienced the impact" or "experienced the impact to an extent" were considered to have experienced the indicated impact (illustrated in Figure 3 and Figure 4).

Overall, over 40% of the participants who experienced appearance change reported becoming passive towards social activities, such as quitting or becoming absent from work or school (42.6%), finding meeting people troublesome (40.2%), and having decreased occasions to leave the house (40.1%). Meanwhile, more than 50% of participants who experienced appearance change also reported maintaining their self-identity even if their appearance changes (55.7%), and having capacity to attend to physical appearance during treatment (55.2%). Results of the chi-square analysis that was performed to examine gender differences indicated the following four items were statistically significant. Females were significantly more distressed than males.

- I did not want to receive pity from others ($\chi^2 = 11.65$, df = 1, $p < 0.001$)
- Decreased occasions to leave the house ($\chi^2 = 13.98$, df = 1, $p < 0.001$)
- Finding meeting people troublesome ($\chi^2 = 36.12$, df = 1, $p < 0.001$)
- Relationship issues with partner became awkward ($\chi^2 = 9.79$, df = 1, $p < 0.001$).

We also conducted a chi-square analysis by dividing into age groups (60 or under and over 60) in order to examine the effect of working age, and significant differences by age were found in nine items.

The following items were significantly higher in those 60 or under than in those over 60.

- I was concerned about my appearance change ($\chi^2 = 7.34$, df = 1, $p < 0.01$).
- I did not want to receive pity from others ($\chi^2 = 15.31$, df = 1, $p < 0.001$).
- Decreased occasions to leave the house

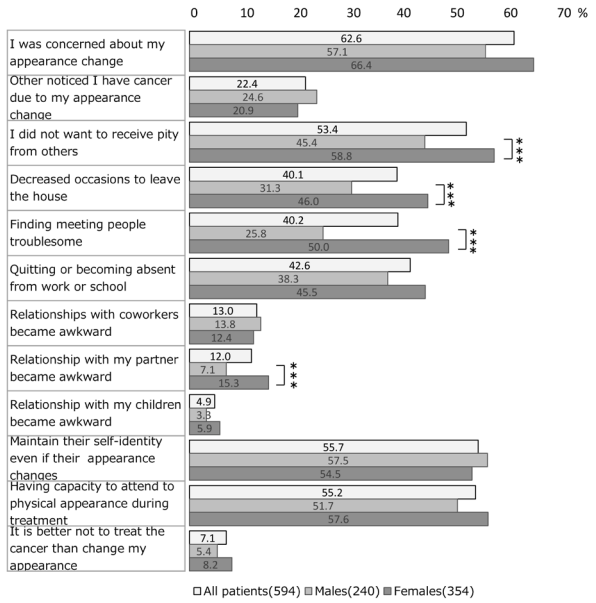

Figure 3. Impact on daily life by gender. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

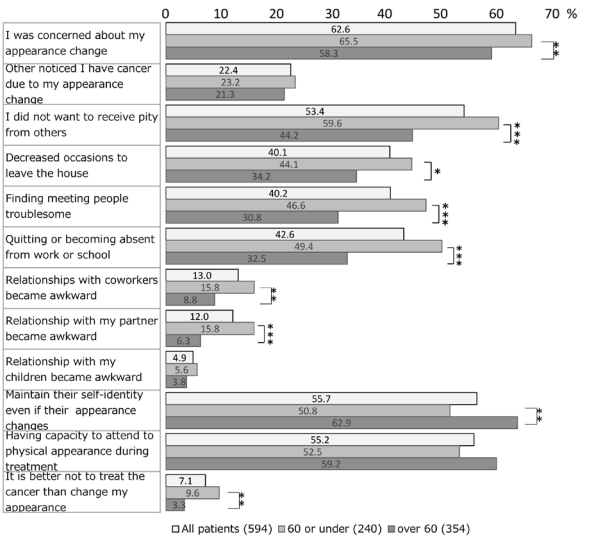

Figure 4. Impact on daily life by age. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

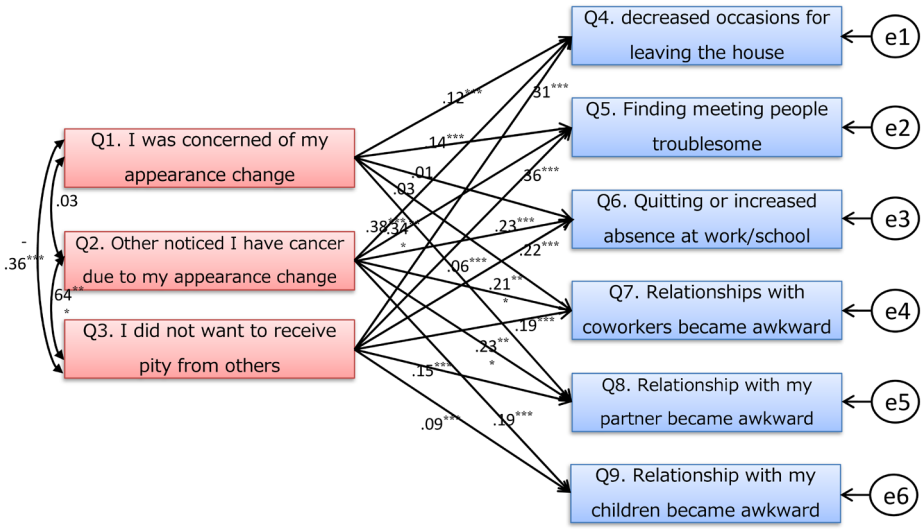

Figure 5. Path analysis with motivation inhibition as the dependent variable. Numbers indicate standardized path analysis coefficients. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

($\chi^2 = 6.51$, df = 1, $p < 0.05$).

- Finding meeting people troublesome ($\chi^2 = 15.80$, df = 1, $p < 0.001$).
- Quitting or becoming absent from work or school ($\chi^2 = 18.10$, df = 1, $p < 0.001$).
- Relationships with coworkers became awkward ($\chi^2 = 7.41$, df = 1, $p < 0.01$).
- Relationship with my partner became awkward ($\chi^2 = 13.25$, df = 1, $p < 0.001$).
- It is better not to treat the cancer than change my appearance ($\chi^2 = 9.29$, df = 1, $p < 0.01$).

On the contrary, the following item was significantly higher in those over 60.

- Maintain their self-identity even if their appearance changes ($\chi^2 = 8.57$, df = 1, $p < 0.01$).

Concerns about changes in physical appearance and its impact on behavior inhibition

A covariance structured analysis using statistical software Amos 16.0 was conducted to examine the impact of concerns about appearance change on behavior inhibition and negative changes in relationships.

The causal model envisaged is that concerns about changes in physical appearance (Q1-3) impact actual life (behavior inhibition in daily life, *etc.*: Q4-9). The final model with the best fit is shown in Figure 5.

For the model fit to the data, Goodness of Fit Index [GFI] =1.000, Adjusted Goodness of Fit Index [AGFI] =1.000 and Root Mean Square Error of Approximation [RMSEA] = 0.000. The standard partial regression

coefficients show a direct positive effect from Q2 or Q3 to Q4, Q5, Q6, Q7, Q8 and Q9. On the other hand, an effect was observed from Q1 to Q4, Q5 and Q8, but a direct effect was not observed from Q1 to Q6 and Q7.

The effects from Q2 and Q3 on Q4 and Q5 were especially significant. Participants that expressed anxieties such as "I did not want to receive pity from others", and "Others noticed I have cancer due to my appearance change" had decreased outings ($\beta = 0.32$, $\beta = 0.31$, respectively), social interactions ($\beta = 0.29$, $\beta = 0.37$, respectively), and attendance at work/school ($\beta = 0.17$, $\beta = 0.19$, respectively), and increased relationship issues ($\beta = 0.26$, $\beta = 0.25$, respectively).

Discussion

Actual conditions of appearance change due to cancer treatments

Experience of appearance change

Upon sampling the data proportioned to gender and cancer type variables, the overall rate of participants who experienced changes in physical appearance was 58.1%, which is less than previous studies (*5,6*). Additionally, excluding "surgical therapy induced scars", which was experienced by about 50% of participants, all other symptoms were experienced by less than 25% of participants. A study of 1,030 people from the general population showed that 95.2% identified hair loss as the most symbolic side effect of cancer treatment (*18*), and hair loss has consistently been indicated as one of the most prevalent distressing symptoms in past studies (*7*). However, in reality, not all cancer patients undergo treatment with hair loss and the prevalence of hair loss is only 22.2%, which is very low in comparison to common belief. It is essential for accurate information to be delivered in the early stages of treatment so that patients who have just been diagnosed with cancer will not be misled by the negative image and panic. Additionally, there is a significant importance in raising awareness in the general public as well.

This study may have provided a complete picture of the appearance problems faced by cancer patients, unlike previous studies, such as a survey of patients undergoing chemotherapy with hair loss (*6,8,12*), which were conducted only on patients with the symptoms in question.

Distress from appearance change and patient support

Symptoms that were reported with high distress levels were long-term changes that were visible to the patients themselves and others, such as surgical removal of body parts including breasts, limbs, and facial features, stoma, and hair loss, as well as symptoms that have a significant negative impact on patients' activities of daily living such as hand-foot syndrome and symptoms related to the nails.

Examining the relationship between the prevalence of symptoms and distress level from the perspective of patient support, the symptoms can be divided into two separate categories. One category consists of symptoms such as hair loss and edema, which are high in both prevalence and distress level, and support addressing these symptoms is generally a broad category that needs to be prioritized. The other category consists of symptoms of low prevalence but that cause significantly high distress levels such as having a stoma, loss of breast from mastectomy, loss of a body part, hand-foot syndrome, and fingernail detachment. These symptoms require personalized support, which is vital as these symptoms in particular have a direct relationship with decreased body image, self-esteem, and activities of daily living.

One of the interesting findings of this study was the difference in distress levels for similar symptoms. For example, hair loss was reported with a high distress level when it occurred on the head, but not when it was body hair or beard. Similarly for changes in body shape, while weight gain and edema were reported with high distress, weight loss had lower distress levels. This may reflect the value of appearance in contemporary society, i.e., slimming perception that leaner body types are more attractive and obesity has a negative impact on employment (*19-21*) or body hair removal preference (*22,23*). Similar to findings in non-cancer related studies that report higher distress levels for changes in the appearance of areas of the body that are more visible (*24*), surgical scars were often in areas hidden under clothing and were reported with lower distress levels. When examining breast cancer patients only, distress levels were higher for hair loss than mastectomy. It can be assumed that concerns for appearance are not solely based on one's own body image, but deeply interconnected with contemporary societal standards and values, concern for societal acceptance, and as a result of social relationship concerns.

Impact on daily life

When examining the ways appearance change has impacted patients' daily lives, especially activities and ways of thinking, more than 40% of participants had behavioral inhibition such as quitting or being absent from work or school. In particular, women who are more conscious about their physical appearance than men and people of working age (60 or under) who are engaged in social activities were negatively impacted in terms of activities.

Meanwhile, patients were generally able to maintain their self-identity despite changes in their appearance, were able to attend to and take care of their physical appearance, and had high self-worth. This suggests that when healthcare professionals provide patients with support, it would be more effective to support people to

feel that they are able to maintain their self-identity and self-worth despite the struggles of treatment instead of focusing on negative behaviors only.

Concerns about changes in physical appearance and its impact on behavioral inhibition

When beginning this study, it was hypothesized that the concerns patients have about changes in appearance directly impact their behavioral inhibition in daily life. In fact, results from this study showed no relationship between concerns and behavioral inhibition. Instead, the results indicated strong concern about others noticing that they have cancer or being pitied by others due to appearance change decrease social interactions and attendance at work and school and increases difficulties in social relationships (Figure 5). This may be a negative behavioral change that occurs because many patients feel that their changed appearance is a "symbol of cancer that others can see" (*10,15*).

If this is true, when patients report physical symptoms to healthcare professionals there is no resolution if the treatment only focuses on caring for the physical symptoms. There is a need to provide patients with not only treatment of symptoms or coping skills, but also information to change beliefs about cancer and appearance and communication skill education to facilitate relationships with others after appearance changes. This may be in line with the importance of cognitive training, as the degree of appearance change is not necessarily proportional to psychosocial health, as demonstrated in a study of non-cancer disfigurement (*25*). It may also be related to critiques on the globally popular "Look Good… Feel Better" approach that its coping techniques may be too limited (*14*).

Limitations

There are limitations to this study as it examined self-reported retrospective data, and the timeframe from the day of diagnosis to when patients answered the survey was not confirmed. It also lacked information on treatment each patient received, so it is not possible to further analyze the details of treatment. Despite these limitations, using an online survey was beneficial to meet the goal of collecting a wide range of information in relation to appearance issues. Moving forward, we hope to further continue this research by collecting additional details with more conventional methods such as interviews and mail-in surveys to achieve a more elaborate interpretation.

Conclusion

This study clarified the specific symptoms that require prioritized support by healthcare professionals, as well as beneficial specific suggestions for the process of delivering such support. Minimizing side effects and treatment and beauty techniques for camouflaging appearance changes are all important and essential; however, in order to avoid behavioral inhibition, it is important to mitigate patients' underlying concern. There is a need for educational program structures that support effective cognitive transformations and techniques for coping with appearance change, and developing successful experiences in social communication, to mitigate the social struggles patients face in relation to appearance change.

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References

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Akinyemiju TF, *et al*. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study. JAMA Oncol. 2018; 4:1553-1568.
2. Cancer Information Service. National cancer incidence and rates based on the National Cancer Registry, 2016-2019. *https://ganjoho.jp/reg_stat/statistics/stat/summary.html* (accessed February 5, 2022). (in Japanese)
3. National Cancer Center Japan. 3-year Survival Rate for 2012, 5-year Survival Rate for 2009-10 in Hospital-based Cancer Registry in Designated Cancer Hospitals Cancer. *https://www.ncc.go.jp/jp/information/pr_release/2019/0808_1/press_release20190808_1.pdf* (accessed October 20, 2022). (in Japanese)
4. Ministry of Health, Labour and Welfare. Patient survey in 2017 statistical table 7. Average length of stay for discharged patients, by year and major injury/illness category. *https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/dl/toukei.pdf* (accessed October 20, 2022). (in Japanese)

5. Ministry of Health, Labour and Welfare. A survey of implementation of chemotherapy at outpatient and inpatient clinics 2012. *https://www.mhlw.go.jp/stf/shingi/2r9852000002puj1-att/2r9852000002qbfz.pdf* (accessed October 20, 2022). (in Japanese)
6. Nozawa K, Tomita M, Takahashi E, Toma S, Arai Y, Takahashi M. Distress from changes in physical appearance and support through information provision in male cancer patients. Jpn J Clin Oncol. 2017; 47:720-727.
7. Nozawa K, Shimizu C, Kakimoto M, Mizota Y, Yamamoto S, Takahashi Y, Ito A, Izumi H, Fujiwara Y. Quantitative assessment of appearance changes and related distress in cancer patients. Psychooncology. 2013; 22;2140-2147.
8. Dua P, Heiland MF, Kracen AC, Deshields TL. Cancer-related hair loss: A selective review of the alopecia research literature. Psychooncology. 2017; 26:438-443.
9. Choi EK, Kim IR, Chang O, Kang D, Nam SJ, Lee JE, Lee SK, Im YH, Park YH, Yang JM, Cho J. Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. Psychooncology. 2014; 23:1103-1110.
10. Rasmussen DM, Hansen HP, Elverdam B. How cancer survivors experience their changed body encountering others. Eur J Oncol Nurs. 2010; 14:154-159.
11. Ucok O. The meaning of appearance in surviving breast cancer. Human Studies. 2005; 28:291-316.
12. Wallace ML, Harcourt D, Rumsey N, Foot A. Managing appearance changes resulting from cancer treatment: Resilience in adolescent females. Psychooncology. 2007; 16:1019-1027.
13. Taggart LR, Ozolins L, Hardie H, Nyhof-Young J. Look good feel better workshops: A "big lift" for women with cancer. J Cancer Educ. 2009; 24:94-99.
14. Harcourt D, Frith H. Women's experiences of an altered appearance during chemotherapy: An indication of cancer status. J Health Psycho. 2008; 13:597-606.
15. Nozawa K, Toma S, Shimizu C, Iino K. Appearance changes experienced by women with breast cancer undergoing chemotherapy, and the structure of their coping behavior. Journal of Japanese Society of Nursing Science for National Health Services. 2015; 11:13-20. (in Japanese)
16. Nozawa K, Toma S. A survey to access changes in appearance associated with cancer treatment and associated coping behaviors; Survey of 1,035 patients based on incidence rate by gender and cancer site. Journal of Japanese Society of Nursing Science for National Health Services. 2020; 16:15-26. (in Japanese)
17. Foundation for Promotion of Cancer Research. Cancer Statistics. *https://ganjoho.jp/data/reg_stat/statistics/brochure/2017/cancer_statistics_2017_fig_J.pdf* (accessed October 20, 2022). (in Japanese)
18. Toma S, Nozawa K, Uesaka M, *et al*. Internet survey of the general public on knowledge and coping with appearance changes associated with cancer treatment. The 56th Annual Meeting of the Japanese Society for Clinical Oncology. 2018; O52-2. (in Japanese)
19. Wang G, Djafarian K, Egedigwe CA, El Hamdouchi A, Ojiambo R, Ramuth H, Wallner-Liebmann SJ, Lackner S, Diouf A, Sauciuvenaite J, Hambly C, Vaanholt LM, Faries MD, Speakman JR. The relationship of female physical attractiveness to body fatness. PeerJ. 2015; 3:e1155.
20. Ogden J. The psychology of eating: from healthy to disordered behavior. Wiley-Blackwell, New Jersey, US, 2003
21. Sassi F. Obesity and the economics of prevention. Fit Not Fat. OECD, 2010. *https://www.oecd.org/els/health-systems/46044572.pdf* (accessed October 20, 2022).
22. Tiggemann M, Hodgson S. The Hairlessness norm extended: Reasons for and predictors of women's body hair removal at different body sites. Sex Roles. 2008; 59:889-897.
23. Terry G, Braun V. To let hair be, or to not let hair be? Gender and body hair removal practices in Aotearoa/New Zealand. Body Image. 2013; 10:599-606.
24. Kent G, Keohane, S. Social anxiety and disfigurement: The moderating effects of fear of negative evaluation and past experience. Br J Clin Psychol. 2001; 40:23-34.
25. Rumsey N, Clarke A, White P, Wyn-Williams M, Garlick W. Altered body image: appearance-related concerns of people with visible disfigurement. J Adv Nurs. 2004; 48:443-453.

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LETTER

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Trends in surgical treatment for prostate cancer: Analysis of National Database Open Data in Japan

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Abstract: We conducted a study to clarify the trends in surgical treatments for prostate cancer in Japan between 2014 and 2020 by analyzing the National Database (NDB) Open Data in Japan. Intriguingly, the number of patients over 70 years old who underwent robotic-assisted radical prostatectomy (RARP) nearly doubled from 2015 to 2019, while that in those 69 years old and younger remained almost constant during the same period. The increase in the number of patients over 70 years of age may reflect the fact that RARP can be safely applied to elderly patients. With the new development and spread of surgery-assisting robots, we can foresee a further increase in the number of RARPs performed for elderly patients in the future.

***Keywords*:** NDB Open Data, robotic-assisted radical prostatectomy, COVID-19

Prostate cancer is the most common malignancy in men worldwide. In 2018, more than 92,000 Japanese men were diagnosed with prostate cancer (*1*). Prostatectomy is the standard treatment option for organ-confined prostate cancer (*2*), while in recent years, the number of robotic-assisted radical prostatectomy (RARP) has been increasing in Japan after being insured in 2012.

To analyze the recent trends in surgical treatment for prostate cancer in Japan, we investigated the National Database (NDB) Open Data in Japan, which contains receipts (medical fee statements) issued by medical institutions to insurers (*3*). The start of the year in the NDB Open Data is April 1st. Overall, in recent years, the total number of surgeries for prostate cancer has increased, except in 2020. The number of prostatectomies performed reached 24,134 in 2019 (Figure 1A). The decrease in 2020 may be explained by the influence of the COVID-19 pandemic, which caused people to refrain from undergoing medical checkups. Interestingly, the ratio of patients younger than 70 years to those 70 years and older reversed in 2018, with patients aged 70 years and older starting to predominate (Figure 1B).

Herein, we analyzed the number of prostatectomies per 100,000 males from official statistics from Japan (*4*). Of note, the number of prostatectomies increased in those over 70 years of age, while it decreased constantly in populations under 69 years of age (Figure 1C). In Japan, open or laparoscopic prostatectomy accounts for a considerable proportion of cases. To examine the trend in each operative technique, we classified surgeries as either RARP or others (open radical prostatectomy, laparoscopic radical prostatectomy, and minimum incision endoscopic prostatectomy). Intriguingly, the number of patients over 70 years old in RARP group nearly doubled from 2015 to 2019, while that in those 69 years old and younger remained almost constant during the same period. However, we could not clarify the reason for this discrepancy. The increase in the number of patients over 70 years of age may reflect the fact that RARP can be safely applied to elderly patients (*2*).

We further found that 5,501 (22.8%) and 4,338 (22.1%) prostatectomies were performed without the robotic systems in 2019 and 2020, respectively. More than 500 robotic systems have been introduced in Japanese hospitals, and the prevalence of RARP is almost equivalent to that in the United States and England (*5*).

In conclusion, we observed an increasing trend in the number of RARP in elderly patients in Japan since the introduction of robotic surgery. With the new development and spread of surgery-assisting robots, we can foresee a further increase in the number of RARPs performed for elderly patients in the future. In contrast, we did not observe any increase in the number of RARPs performed in patients younger than 69 years.

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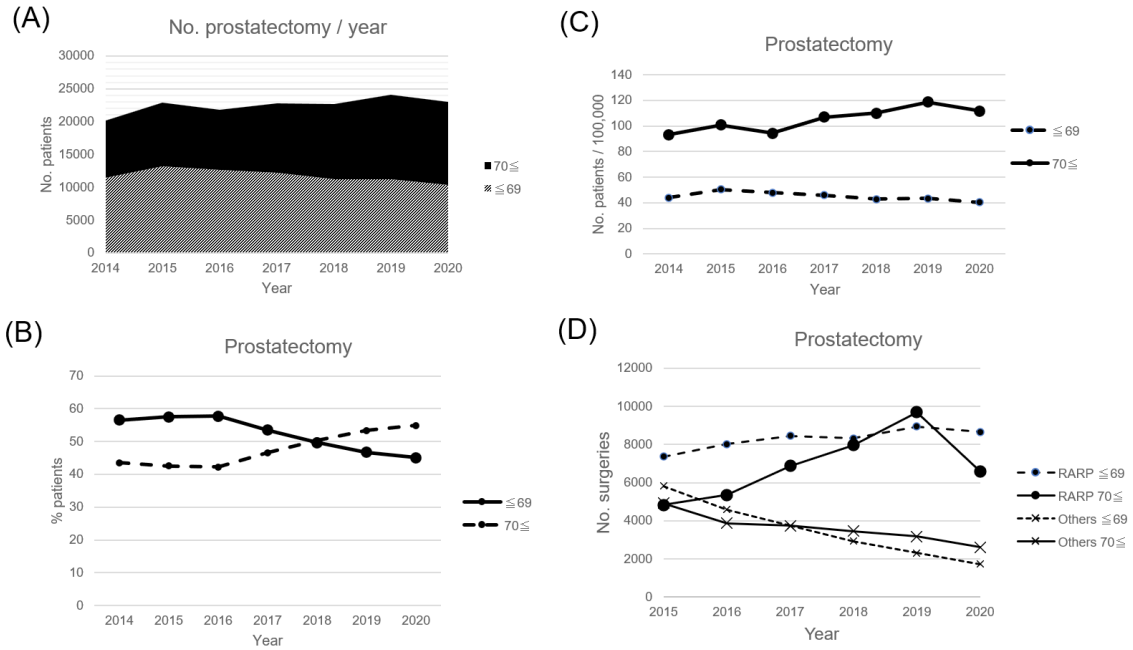

Figure 1. (A) Number of prostatectomies performed per year; (B) Proportion of prostatectomies by age; (C) Number of prostatectomies per 100,000 population; (D) Number of prostatectomies by surgical technique.

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References

1. National Cancer Center. "Prostate cancer". *https://ganjoho.jp/reg_stat/statistics/stat/cancer/20_prostate.html* (accessed October 3, 2022). (In Japanese)
2. Yamada Y, Teshima T, Fujimura T, Sato Y, Nakamura M, Niimi A, Kimura N, Kakutani S, Kawai T, Yamada D, Suzuki M, Kume H. Comparison of perioperative outcomes in elderly (age ≥ 75 years) *vs*. younger men undergoing robot-assisted radical prostatectomy. PLoS One. 2020; 15:e0234113.
3. Ministry of Health, Labour and Welfare. "NDB Open Data". *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html* (accessed October 1, 2022). (In Japanese)
4. e-Stat. "Statistics of Japan". *https://www.e-stat.go.jp* (accessed October 1, 2022). (In Japanese)
5. Maynou L, Mehtsun WT, Serra-Sastre V, Papanicolas I. Patterns of adoption of robotic radical prostatectomy in the United States and England. Health Serv Res. 2021; 56(Suppl 3):1441-1461.

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LETTER
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Theoretical and evidence-based infection control during general anesthesia in the COVID-19 pandemic

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Abstract: With the outbreak of COVID-19, attention has focused on measures to prevent droplet infection. Operating rooms, where we anesthesiologists mainly work, are equipped with various theories and techniques for performing surgical procedures and general anesthesia on patients with various infectious diseases, whether airborne, droplet, or contact infection, and are an environment where surgical procedures and general anesthesia can be safely performed on patients with compromised immune functions. Here, we describe the anesthesia management standards assuming COVID-19 from the viewpoint of medical safety, as well as the structure for supplying clean air in the operating room and the structure of a negative-pressure operating room.

***Keywords*:** COVID-19, general anesthesia, operating room

The COVID-19 pandemic has drawn attention to droplet infection control measures. Various methods have been devised to protect against droplet infection, including not only surgical masks but also acrylic plates and film sheets, and detection of poorly ventilated areas by measuring CO_2 concentrations, but their effectiveness remains unclear. In addition, although a simulation of droplet dispersion using the Japan's supercomputer Fugaku has attracted much attention, we cannot verify whether the various preconditions are general or not, and it is very doubtful whether we can really apply them to our living and working environments.

In the operating room environment where we anesthesiologists mainly work, we have established an environment in which surgical procedures and general anesthesia can be safely performed on surgical patients with impaired immune functions through many years of research and efforts to improve the environment. In addition, various theories and techniques for performing surgical procedures and general anesthesia on patients with various infectious diseases, whether airborne, droplet, or contact infection, have been developed, and evidence has already been established on how to deal with them. Therefore, if these theories and techniques are properly applied, general anesthesia can be administered with ease even to patients with SARS-CoV-2 infection and other unknown infectious diseases.

Environmental features of operating room

In the operating room for surgery, clean air is supplied from the ceiling, and air contaminated by the patient is collected from the air intake under the feet. In general operating rooms in Japan (air clean level 2), clean air is supplied at a rate at which the air in the operating room is replaced in about 4 minutes (*1*). But in reality, the air is not actually supplied at a uniform rate due to the installation of the ceiling light, some devices in the operating room, operating tables, and so on. Therefore, it is important to identify and remove obstacles so that medical personnel can avoid the risk of inhaling contaminated air emitted from patients by using test smokes used in the occupational safety domain (Figure 1). The effectiveness of acrylic panels in preventing the spread of droplets from the patient should also be evaluated for actual airflow. Unfortunately, the measurement of CO_2 concentration used in some situations can only predict air stagnation by measuring the CO_2 contained in exhaled air, but cannot evaluate air movement. Unfortunately, it is not possible to assess the movement of air. To begin with, a situation in which air is stagnant is out of the question from the perspective of ventilation or airflow management, and a more appropriate environment should be created.

To ensure the airflow created in the operating room, it is essential to minimize the number of people in the operating room as well as entering and leaving the operating room. For this reason, even if COVID-19 is not in its infestation period, strict control is required to limit the entry of visitors and minimize the opening and closing of the doors of each operating room. In particular, bio-clean rooms (air clean level 1) are equipped with a front chamber, and a system is used to prevent the simultaneous opening of doors on the operating room

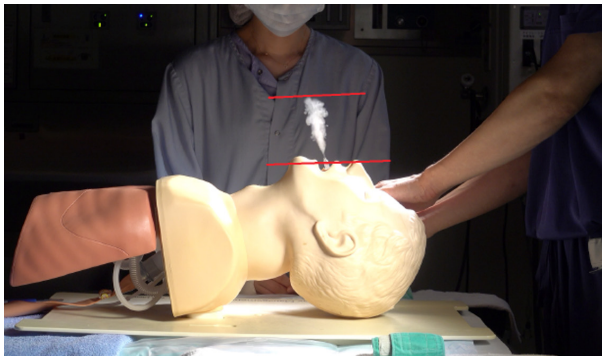

Figure 1. Image of Airflow with test smokes. The airflow in the operating room can be evaluated under various conditions using a test smoke that simulates the patient's exhalation.

side and the corridor side.

Use of negative-pressure operating rooms to reduce leakage of contaminated air

As in patients with common infectious complications, invasive procedures are known to worsen the prognosis in patients with SARS-CoV-2 infection. As a rule, invasive procedures should be performed only after the infectious disease is cured. On the other hand, invasive procedures are exceptionally performed under general anesthesia in life-threatening emergent surgeries. In such situations, a negative-pressure operating room is used to prevent contaminated air generated by the infectious patient from leaking out of the operating room. In a normal operating room, clean air is supplied from the ceiling, so the air pressure is higher than that in the corridor. In a negative-pressure operating room, however, air is collected from the air intake under the feet so that the air pressure in the operating room is lower (*i.e.* negative pressure) than that in the corridor to prevent contaminated air from leaking into the corridor side. It should be understood that a negative-pressure operating room draws air from the corridor, which has the lowest level of air cleanliness in a medical facility. Since surgery is performed in an unclean environment, the use of negative-pressure operating rooms should be limited to unavoidable cases, and patients will be at a great disadvantage if they are used easily because they are suspected of having an infectious disease.

Standards of anesthesia management to prioritize protection of the surgical patient

In patients with SARS-CoV-2 infection, risk of perioperative mortality increased throughout 6 weeks of infection (*2*), and patients should avoid elective surgery within 7 weeks after the presence of infection, even if asymptomatic. In addition, the anesthesiologist should determine the waiting period from the viewpoint of recovery of the respiratory and other systemic conditions in patients with moderate disease whose general condition has not yet recovered, and in patients on ECMO or ventilatory management (*3*). It is important that this does not mean that the risk of infection to the surrounding population, including health care workers, continues until 7 weeks later. From an infectious point of view, elective surgery should not take place within 10 days of diagnosis (*3*). In patients with recent or preoperative infection with SARS-CoV-2, surgery under local anesthesia should be considered, avoiding general anesthesia.

If a patient scheduled for surgery shows signs of infection, such as fever, before surgery, surgery should generally be postponed. This is because fever itself is a risk for perioperative complications, not the presence or absence of SARS-CoV-2 infection, which determines whether general anesthesia can be performed or not. From the viewpoint of medical safety, it is fundamentally wrong to think that surgery can be performed because the PCR test is negative.

Causes of unfortunate events

This article has focused on the structure of the operating room, the negative pressure operating room, and the latest perioperative management guidelines, but faithful adherence to the items described here will help control risk and achieve stable perioperative management. However, as we have seen in various media reports, lack of basic medical knowledge, human error, local rules at each facility that pervert the evidence, and irrational and emotional on-site judgment have caused confusion in clinical practice. The job of anesthesiologists is expressed to be crisis management. In order to respond appropriately not only to COVID-19 but also to newly emerging infectious diseases, it is essential to follow the basic procedure of crisis management, which is to take the maximum possible measures at first, and then to accumulate the necessary measures while reducing excessive measures based on the knowledge obtained later.

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References

1. Healthcare Engineering Association of Japan. Hospital Equipment Design Guidelines (Air conditioning volume) HEAS-02-2013. Tokyo: Healthcare Engineering Association of Japan; 2013. (in Japanese)
2. COVIDSurg Collaborative; GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia. 2021; 76:748-758.
3. El-Boghdadly K, Cook TM, Goodacre T, Kua J, Denmark S, McNally S, Mercer N, Moonesinghe SR, Summerton

DJ. Timing of elective surgery and risk assessment after SARS-CoV-2 infection: an update: A multidisciplinary consensus statement on behalf of the Association of Anaesthetists, Centre for Perioperative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists, Royal College of Surgeons of England. Anaesthesia. 2022; 77:580-587.

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Global Health & Medicine

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We encourage submission of original research findings in the fields of global health, public health, and health care delivery as well as the seminal and latest research on the intersection of biomedical science and clinical practice.

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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.

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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

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.

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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.

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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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