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Factors associated with withholding of invasive mechanical ventilation in the early phase of the COVID-19 response and their ethical analyses

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Abstract: End-of-life decision making regarding invasive mechanical ventilation (IMV) for patients with severe coronavirus disease (COVID-19) is challenging. We aimed to explore the factors associated with the withholding of IMV in patients with COVID-19. This retrospective study included patients registered in a nationwide COVID-19 Registry Japan. We enrolled patients with COVID-19 admitted between January 1, 2020, and June 30, 2021, and died during hospitalization. The enrolled patients were divided into two groups: those who received IMV (IMV group) and those who did not (non-IMV group). To identify the factors associated with withholding of IMV among patients with COVID-19 who died during hospitalization, we conducted a multivariate logistic regression analysis. A total of 2,401 patients were enrolled. Of these, 588 (24.5%) were in the IMV group and 1813 (75.5%) in the non-IMV group. Withholding IMV was positively associated with older age (95% confidence interval [CI]: 0.82–0.88, $p < 0.0001$), dementia (95% CI: 0.81–0.91, $p < 0.0001$), chronic lung disease (95% CI: 0.88–1.00, $p = 0.036$), and malignancy (95% CI: 0.82–0.94, $p < 0.0004$) although inversely associated with male sex (95% CI: 1.04–1.15, $p = 0.0008$), body mass index (95% CI: 1.01–1.02, $p < 0.0001$), and National Early Warning Score (95% CI: 1.01–1.03, $p < 0.0001$). We subsequently analyzed these results to inform preparedness for future emerging infectious disease pandemics by retrospectively examining the decision-making processes during the COVID-19 crisis, with particular attention to the role of multidisciplinary collaboration. Based on this study, it will be essential in future pandemics to assess decisions concerning life-sustaining treatments, including IMV, from both scientific and ethical perspectives.

***Keywords*:** decision-making, end-of-life, severe COVID-19, principles of biomedical ethics

Introduction

End-of-life decision making is challenging among patients with severe coronavirus disease (COVID-19). One of the clinical features of COVID-19 is the sudden progression of respiratory failure around the 7th day of onset (*1*), which does not allow medical staff adequate time to discuss treatment goals and plans with patients and their families. Moreover, family members are often unable to communicate because of their own infection and hospital visitation restrictions, which further complicate the decision-making process (*2*). In addition, there was little evidence on the management of COVID-19, especially in the early phases of the COVID-19 response (*3,4*). Critical care teams may experience ethical challenges when making decisions about whether to intubate patients with COVID-19, as their prognosis is uncertain and the availability of ventilators and critical care beds may be limited (*5*). The decision to perform tracheal intubation within a limited period is challenging for healthcare providers.

In this study, we explored the factors associated with the withholding of invasive mechanical ventilation (IMV) to prepare for future emerging infectious disease pandemics by retrospectively examining the treatment decision-making process during the

COVID-19 pandemic and considering multidisciplinary collaboration, including palliative care teams.

Materials and Methods

Study design

This retrospective study included patients registered in a nationwide Japanese registry, COVID-19 Registry Japan (COVIREGI-JP) (*4*). In this registry, patients diagnosed with COVID-19 (positive for severe acute respiratory syndrome coronavirus-2 rapid antigen or polymerase chain reaction test) and hospitalized in 641 participating healthcare facilities were enrolled. Research collaborators at each facility manually input data into the registry by referring to medical records. The study data were collected and managed using REDCap (Research Electronic Data Capture), a secure web-based data capture application hosted at JCRAC data center of the National Center for Global Health and Medicine. The study protocol was reviewed and approved by the Research Ethics Committee of the National Center for Global Health and Medicine (NCGM) (NCGM-G-003494-0). The study was conducted in accordance with the principles of the Declaration of Helsinki. The opt-out recruitment method was applied, and informed consents for individuals were waived as approved by the NCGM Ethics Review.

Patients

Of the patients registered in COVIREGI-JP, we enrolled patients with COVID-19 admitted between January 1, 2020, and June 30, 2021, and died during hospitalization. The enrolled patients were divided into two groups: patients who received IMV (IMV group) and patients who did not receive IMV (non-IMV group).

Variables investigated

Patient demographics, including sex, age, smoking and drinking history, and underlying medical conditions, were investigated. The National Early Warning Score (NEWS) is a validated early warning scoring system comprising six physiological measurements (respiratory rate, oxygen saturation, body temperature, systolic blood pressure, heart rate, and level of consciousness) used to assess patients at risk of early exacerbation. The NEWS determines the triage category for a clinical alert, requiring clinician assessment based on the following score levels: low (1–4), medium (5–6), and high (7 or more) (*6*). Respiratory support with the highest dose of oxygen during hospitalization was classified into five categories: no oxygen, cannula/mask/reservoir, nasal high-flow, non-invasive positive pressure ventilation, and artificial respirator. Medical burden/distress was assessed based on the state of emergency at hospital admission. In addition, transfer from other institutions and the number of days from symptom onset to admission, days from admission to IMV, and days from admission to death were investigated.

Statistical analysis

Categorical variables are presented as counts (%), while continuous variables are presented as median and interquartile range (IQR). Fisher's exact test was used for categorical variables and Wilcoxon rank sum test for continuous variables. To identify the factors associated with withholding IMV in patients with COVID-19 who died during hospitalization, we conducted a multivariate logistic regression analysis and obtained adjusted odds ratios (ORs) with 95% confidence intervals (CIs). We included participant characteristics and disease severity (age, sex, body mass index [BMI], high-risk comorbidity, and NEWS) as independent variables according to the clinical implications and previous literature (*7*).

The level of significance for all statistical tests was set at $\alpha = 0.05$. Data were analyzed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2,401 patients were enrolled in this study. Of these, 588 (24.5%) were in the IMV group and 1813 (75.5%) in the non-IMV group. Patient demographics, NEWS on admission, state of emergency at hospital admission, respiratory support with the highest dose of oxygen during hospitalization, days from symptom onset to admission, transfer from another institution, days from admission to IMV, and days from admission to death are shown in Table 1. Among the patients, 1,469 (61.2%) were male. The median age of the IMV group was lower than that of the non-IMV group (74 *vs.* 85 years, $p < 0.001$). The median BMI was higher in the IMV group than in the non-IMV group (24.3 *vs.* 21.6, $p < 0.001$). In the IMV group, 151 patients (25.9%) did not receive oxygen support upon admission. Two hundred and forty-nine patients (42.3%) in the IMV group and 829 patients (45.7%) in the non-IMV group were admitted during the state of emergency ($p = 0.161$). The median number of days (IQR) from onset to admission in the IMV and non-IMV groups were 2 (0, 5) and 6 (3, 9) days, respectively ($p < 0.001$). Two hundred and fifty patients (43.3%) in the IMV group and 306 (17.3%) in the non-IMV group were transferred from other healthcare facilities ($p < 0.001$). The median number of days (IQR) from admission to IMV in the IMV group was 1 (0, 5). The median number of days (IQR) from admission to death in the IMV and non-IMV groups were 20 (12, 32) and 14 (8, 24), respectively ($p < 0.001$).

The results of the multivariate logistic regression

Table 1. Patient demographics, NEWS on admission, state of emergency at hospital admission, respiratory support with the highest dose of oxygen during hospitalization, days from symptom onset to admission, transfer from another institution, days from admission to IMV, and days from admission to death (n = 2,401)

		Non-IMV group	IMV group	Total	p value
Number of patients		1,813	588	2,401	
Demographics					
Sex	Male[a]	1,045 (57.6)	424 (72.1)	1,469 (61.2)	< 0.001
	Female[a]	768 (42.4)	164 (27.9)	932 (38.8)	
Age	Median [IQR]	85 [79, 90]	74 [68, 80]	83 [76, 88]	< 0.001
Smoking history (former or current smoker)	*n*, (%)[a]	505 (27.9)	248 (42.2)	753 (31.4)	< 0.001
Drinking alcohol (daily or occasionally)	*n*, (%)[a]	276 (15.4)	165 (28.9)	441 (18.6)	< 0.001
BMI	Median [IQR]	21.6 [19, 24.4]	24.3 [22, 27]	22.5 [19.5, 25.3]	< 0.001
Days from symptom onset to admission	Median [IQR]	2 [0, 5]	6 [3, 9]	3 [1, 7]	< 0.001
Transfer from other institution	*n*, (%)[a]	306 (17.3)	250 (43.3)	556 (23.7)	< 0.001
Admission to ICU	*n*, (%)[a]	220 (12.1)	495 (84.2)	715 (29.8)	< 0.001
Days from admission to ICU	Median [IQR]	0 [0, 3]	0 [0, 2]	0 [0, 3]	0.13
Days from admission to IMV	Median [IQR]	N/A	1 [0, 5]	1 [0, 5]	-
Days from admission to death	Median [IQR]	14 [8, 24.2]	20 [12, 32]	15 [9, 27]	< 0.001
Underlying medical conditions					
Myocardial infarction/Congestive heart failure	*n*, (%)[a]	364 (20.1)	77 (13.1)	441 (18.4)	< 0.001
Cerebrovascular disease	*n*, (%)[a]	385 (21.2)	76 (12.9)	461 (19.2)	< 0.001
Paralysis	*n*, (%)[a]	89 (4.9)	12 (2)	101 (4.2)	0.001
Dementia	*n*, (%)[a]	633 (34.9)	42 (7.1)	675 (28.1)	< 0.001
COPD or other lung disease	*n*, (%)[a]	295 (16.3)	95 (16.2)	390 (16.2)	0.943
Liver disease	*n*, (%)[a]	79 (4.4)	29 (4.9)	108 (4.5)	0.552
Hypertension	*n*, (%)[a]	890 (49.1)	296 (50.3)	1,186 (49.4)	0.600
Diabetes Mellitus	*n*, (%)[a]	506 (27.9)	233 (39.6)	739 (30.8)	< 0.001
CKD or HD	*n*, (%)[a]	165 (9.1)	75 (12.8)	240 (10)	0.013
Malignancy	*n*, (%)[a]	304 (16.8)	63 (10.7)	367 (15.3)	< 0.001
HIV/AIDS	*n*, (%)[a]	2 (0.1)	0 (0)	2 (0.1)	1.000
Conditions at admission					
NEWS	0-4 *n*, (%)[a]	567 (31.3)	139 (23.6)	706 (29.4)	< 0.001
	5-6 *n*, (%)[a]	280 (15.4)	124 (21.1)	404 (16.8)	
	7 *n*, (%)[a]	424 (23.4)	221 (37.6)	645 (26.9)	
	Unknown *n*, (%)[a]	542 (29.9)	104 (17.7)	646 (26.9)	
Maximum oxygen support during hospitalization	No oxygen *n*, (%)[a]	63 (3.5)	0 (0)	63 (2.6)	< 0.001
	Canula/Mask/Reservoir *n*, (%)[a]	1,356 (77.5)	0 (0.0)	1,356 (58)	
	Nasal high-flow *n*, (%)[a]	320 (18.3)	0 (0.0)	320 (13.7)	
	Non-invasive positive pressure ventilation *n*, (%)[a]	74 (4.2)	0 (0.0)	74 (3.2)	
	Artificial respirator *n*, (%)[a]	0 (0.0)	531 (90.3)	531 (22.7)	
State of emergency on admission	*n*, (%)[a]	829 (45.7)	249 (42.3)	1,078 (44.9)	0.161

[a]The denominator in each category depends on the number of missing values. Abbreviations: IMV, invasive mechanical ventilation; NEWS, National Early Warning Score; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; N/A, not available; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HD, hemodialysis; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

analysis, including ORs and 95% CIs, of the factors associated with withholding IMV among patients with COVID-19 who died during hospitalization are shown in Table 2. Withholding IMV was positively associated with older age (0.85, 95% CI: 0.82–0.88, $p < 0.0001$), dementia (0.86, 95% CI: 0.81–0.91, $p < 0.0001$), chronic lung disease (0.94, 95% CI: 0.88–1.00, $p = 0.036$), and malignancy (0.88, 95% CI: 0.82–0.94, $p < 0.0004$), but was inversely associated with male sex (1.09, 95% CI: 1.04–1.15, $p = 0.0008$), BMI (1.02. 95% CI: 1.01–1.02, $p < 0.0001$), and NEWS (1.02, 95% CI: 1.01–1.03, $p < 0.0001$).

Discussion

We analyzed the results obtained in this study based on the four principles of biomedical ethics: respect for autonomy, non-maleficence, beneficence, and justice (*8*). The first principle requires medical professionals to respect the autonomous choices of patients, the second to do no harm to patients, the third to provide clinical benefits to patients, and the fourth to distribute burdens, benefits, and opportunities in a fair, equitable, and appropriate way. Although some authors have pointed out their limitations such as their applicability in actual

Table 2. Factors associated with the withholding of invasive mechanical ventilation in the early phase of COVID-19 response — Multivariable logistic regression (*n* = 2,401)

Variables	Odds ratio	95% CI	*p* value
Age	0.85	[0.82, 0.88]	< 0.0001
Sex Male	1.09	[1.04, 1.15]	0.0008
BMI	1.02	[1.01, 1.02]	< 0.0001
NEWS	1.02	[1.01 1.03]	< 0.0001
Myocardial infarction/Congestive heart failure	1.00	[0.94, 1.06]	0.9202
Cerebrovascular disease	0.95	[0.89, 1.01]	0.1279
Paralysis	0.93	[0.81, 1.06]	0.2673
Dementia	0.86	[0.81, 0.91]	< 0.0001
COPD or other lung disease	0.94	[0.88, 1.00]	0.0360
Liver disease	1.05	[0.94, 1.17]	0.3732
Hypertension	1.00	[0.95, 1.05]	0.9847
Diabetes Mellitus	1.04	[0.99, 1.09]	0.1684
CKD or HD	1.01	[0.93, 1.09]	0.8750
Malignancy	0.88	[0.82, 0.94]	0.0004
HIV/AIDS	0.60	[0.34, 1.05]	0.0757
State of emergency on admission	0.97	[0.34, 1.05]	0.1713

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; BMI, body mass index; NEWS, National Early Warning Score; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HD, hemodialysis; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

situations, no bioethicist can deny that the principles have been very influential in the field of bioethics or medical ethics and have been used worldwide since 1979 (*9,10*). In addition, according to some bioethicists, the principles "afford a good and useful moral framework for practicing good medical ethics" (*11*).

First, patients in the IMV group were intubated for a median of 1 day after admission. The rate of transfer from other institutions was 17.3% in the non-IMV group and 43.3% in the IMV group. It is possible that patients were transferred for intensive care, including intubation management, which may explain why patients in the IMV group were intubated early (median, 1 day) after admission.

Although there is a flowchart for allocating ventilators in COVID-19 care (*12*), in reality, many cases cannot be covered by the flowchart owing to individual circumstances. In particular, decision-making immediately after the arrival of critically ill patients is challenging (*13,14*). Physicians have a professional duty to pursue the best interests of their patients, which implies that they should adhere to the principle of beneficence. However, physicians must consider not only the clinical benefits of patients from a medical standpoint but also the patient's own view of life and values (*13*). In this case, patients must express their own values and make choices of medical treatment; however, chances are that they lack a clear understanding of their own values. If that is the case, physicians must then hold a conversation with the patient and understand the patient's intentions. This process is also linked with respect for the patient's autonomy. With regard to the principle of respect for autonomy, physicians and patients should discuss their attitudes towards a disease and treatment (*15*). If the patient is unconscious and incapable of making decisions, physicians have no choice but to infer the patient's intention through proxy/surrogate decision-making by family members and relatives. Among patients with COVID-19, however, it is difficult to discuss goals of care in cases of rapidly progressing respiratory failure (*16*). Moreover, sufficient discussion with the patient on the decision to implement IMV is not always possible due to the rapid progression of the disease (*17*) and limited opportunities for face-to-face discussion (*2*). Furthermore, the family member who could serve as a surrogate is isolated following exposure to the disease (*18*). In consequence, the medical professionals have difficulty in communicating adequately with patients and their families during the acute stage of COVID-19. It is thus possible to infer that the physicians may end up giving priority to the principle of beneficence, or that of nonmaleficence in severe and life-threatening cases over the principle of respect for autonomy in such a situation where urgent medical decision to provide IMV is needed (*19*).

Second, older age, dementia, underlying chronic lung disease, and malignancy were associated with withholding IMV. From a medical perspective, advanced age, underlying lung disease, and malignancy are risk factors for COVID-19 severity and mortality. When intubated, the mortality rate was 34.8% for patients aged 65–74 years, 43.5% for those aged 75–89 years, and 75% for those aged 90 years. Mortality rates were 29.8% and 38.3% in patients with chronic lung disease and malignancy, respectively (*4*). Patients with these characteristics have a high mortality rate even if IMV is performed, and it is unlikely that IMV would be of clinical benefit to them. In light of the principles of beneficence, there is little rationale for performing IMV in older patients with underlying chronic lung diseases and malignancies. Moreover, since IMV is an invasive procedure, and considering the "do no harm to patients" principle or the principle of nonmaleficence, IMV should be avoided if possible. Thus, performing IMV in older patients, those with underlying chronic lung disease, or those with malignancy is not only unlikely to provide clinical benefit but is also likely to impair clinical benefit, that is, increase the risk of adverse health outcomes. Therefore, it is possible to infer that the healthcare providers tend to withhold IMV from older patients and those with underlying chronic lung disease or malignancy. However, the range of malignant conditions varies between patients undergoing curative postoperative chemotherapy and those in the terminal stages of the disease, underscoring the need for individualized decision-making.

Dementia has also been reported as an independent risk factor for mortality (*20*). Since it is difficult to obtain informed consent from patients with dementia, the focus shifts to the patient's family members or relatives who can provide proxy consent for IMV. However, as mentioned above, it is difficult to have a discussion with the patient's family members and relatives in the acute phase of COVID-19. Therefore, it can be inferred that for patients with backgrounds, such as advanced age, dementia, underlying chronic lung disease, and malignancy, the principles of beneficence and nonmaleficence, rather than the principle of respect for autonomy, took precedence in medical practice, resulting in a tendency to avoid IMV.

Third, non-obese status and female sex were associated with withholding of IMV. These results may be due to several reasons. One, as obesity and male sex are risk factors for severe COVID-19, women with non-obese status are at a lower risk of severe disease and are less likely to develop respiratory failure. Therefore, the clinical benefits of IMV may have been judged to be low. Given the principle of beneficence, there is little rationale for aggressively implementing IMV. Moreover, as IMV is an invasive procedure, it should be avoided according to the principle of nonmaleficence. Thus, IMV in non-obese women was possibly withheld because of its low clinical benefit and high risk of adverse health outcomes. Two, IMV was also withheld in older, non-obese, and female patients. Even with the additional condition of "older age," perhaps the COVID-19 was not yet severe at admission, and there was adequate time after admission to discuss the treatment plan, including IMV, with healthcare providers. In addition, "older, non-obese, and female" patients comprise the majority of residents in long-term nursing care facilities. In Japan, older people with advanced frailty and reduced oral intake are often thin, and women tend to have a longer life expectancy (*21*). These women may have discussed their end-of-life treatment plans with family members and facility staff in advance and may have expressed their intentions in writing. For example, although not in the COVID-19 era, a previous study found that the rate of advance directives was high among nursing home residents and hospice users aged ≥ 65 years (*22*) and more women than men provided do not attempt resuscitation instructions (*23,24*). In the present study, patients may have heard news reports about the situation and treatment options in the COVID-19 pandemic, considered which treatment options they would like, and indicated some preferences for medical measures after hospitalization, either in advance or at admission. Three, in older patients, even if respiratory failure is not caused by COVID-19, patients may die because of exacerbation of the underlying disease or complications triggered by COVID-19 (*25*). It is possible that there were cases in which the underlying disease worsened or complications developed after admission, and IMV was not indicated in these cases.

Fourth, the participants of this study were patients in the first through fourth waves of COVID-19. During this period, the capacity to accept patients with severe COVID-19 was always greater than the actual number of patients with COVID-19 on ventilators nationwide (*26*). There was no obvious depletion of medical equipment, such as ventilators (*21,22*), nor reports that the capacity of intensive care was exceeded. Of note, there was fair allocation of medical resources at the macro, meso, and micro levels (*27*), with no reports suggesting otherwise. Thus, the principle of justice may be irrelevant to the results of this study.

However, although the number of beds notified to the government was secured, the actual supply-demand balance was tight, as requests were not easily met in the medical wards and intensive care units (*28*). For example, many deaths occurred in Japan for the first time in the fourth wave (*29*), which may reflect resource constraints in medical facilities. Therefore, whether access to ventilators was sufficient during the extreme phase of the COVID-19 pandemic should be further considered.

Our study has several limitations. First, we lacked data on the presence or absence of advance care planning (ACP) prior to infection, the decision-making process at admission, and the patients' own wishes. Therefore, we could not examine whether patients received the care they wanted (goal-concordant care) and the decision-making regarding ACP immediately after admission.

Second, we only included patient factors as explanatory variables, and withholding life-sustaining treatments involves a complex set of factors, including factors related to the healthcare provider and medical institution. Future research should include these factors as explanatory variables.

Third, we could not identify the reasons for withholding IMV in this study; we could not evaluate every unique patient scenario with the ethical considerations. Future research should explore the reasons for withholding IMV in each patient.

Fourth, we did not assess frailty scores in this study. Frailty and older age have been reported to be the greatest predictors of COVID-19 mortality (*30*). Given that IMV tended to be withheld in women with non-obese status, frailty may be a confounding factor. Therefore, further studies are warranted.

Fifth, patients with COVID-19, especially the older patients, die from exacerbation of the original underlying disease or complications triggered by COVID-19. Especially after the omicron strain, most patients died of exacerbation of the original underlying disease or complications, whereas patients infected with the delta strain died of respiratory failure due to COVID-19 pneumonia (*25*). In this study, we focused on patients from the first through fourth waves (alpha strain was dominant), and most patients died of respiratory failure due to COVID-19 pneumonia.

Finally, although this study included a large number of COVID-19 inpatients in Japan, there may have been some selection bias for inclusion, as noted above, and due to the manual input of the data. Thus, the study results may not accurately reflect the actual status of the general Japanese population hospitalized for COVID-19 (*1*).

In conclusion, we explored patient factors and data associated with the withholding of IMV and analyzed the results based on the four principles of biomedical ethics by taking a retrospective look at the treatment decision-making process in the COVID-19 disaster and considering multidisciplinary collaboration, including palliative care teams. This study indicates that none of the results significantly diverged from the four principles, although this alignment may be coincidental. Building on these findings, we recommend that future pandemic preparedness efforts incorporate a systematic, preemptive evaluation of decision-making concerning life-sustaining interventions — such as IMV — from both scientific and ethical perspectives, including the four principles of biomedical ethics.

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