Association between mortality and age among mechanically ventilated COVID-19 patients: a Japanese nationwide COVID-19 database study

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Abstract
Background: Only a few studies have reported the association between age and mortality in COVID-19 patients who require invasive mechanical ventilation (IMV). We aimed to evaluate the effect of age on COVID-19-related mortality among patients undergoing IMV therapy.

Methods: This cohort study was conducted using the COVID-19 Registry Japan database, a nationwide multi-centre study of hospitalized patients with laboratory-confirmed COVID-19. Of all 33,808 cases registered between 1 January 2020 to 28 February 2021, we analysed 1555 patients who had undergone IMV. We evaluated mortality rates between age groups using multivariable regression analysis after adjusting for known potential components, such as within-hospital clustering, comorbidities, steroid use, medication for COVID-19, and vital signs on admission, using generalized estimation equation.

Results: By age group, the mortality rates in the IMV group were 8.6%, 20.7%, 34.9%, 49.7% and 83.3% for patients in their 50s, 60s, 70s, 80s, and 90s, respectively. Multivariable analysis showed that compared with those for patients aged < 60 years, the odds ratios (95% confidence interval) of death were 2.6 (1.6–4.1), 6.9 (4.2–11.3), 13.2 (7.2–24.1), 92.6 (16.7–515.0) for patients in their 60s, 70s, 80s, and 90s, respectively.

Conclusions: In this cohort study, age had a great effect on mortality in COVID-19 patients undergoing IMV, after adjusting for variables independently associated with mortality. This study suggested that age was associated with higher mortality and that preventing progression to severe COVID-19 in elderly patients may be a great public health issue.

Keywords: COVID-19, Age, Mechanical ventilation, Mortality

Background
In December 2019, the first case of the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in Wuhan, China [1]. The first COVID-19 case in Japan was reported on 16 January, 2020, and the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [2, 3]. Currently, the
clinical spectrum of COVID-19 ranges from mild to severe, and the mortality rates of patients with severe cases undergoing invasive mechanical ventilation (IMV) are reportedly high [4–6]. Several studies have identified older age as an independent prognostic factor for mortality [4, 7–13]; however, limited information is available on the relationship between mortality and critically ill patients on IMV, stratified by age group [6, 7].

In Japan, people aged > 65 years accounted for 28.7% of the total population in 2020, and the number of frail elderly individuals has been increasing with advancing age. Moreover, Japan was confronted with a shortage of beds, staff members, and ventilators during the peak of the COVID-19 pandemic. Therefore, the association between age and mortality is an important clinical issue, especially in an aging society, in deciding whether to perform IMV therapy for older adults.

We aimed to investigate the patterns of in-hospital mortality among critically ill patients with COVID-19 who required IMV, by age group, in Japan, while adjusting for other factors related to mortality.

Methods

Ethics approval
The present study adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Nippon Medical School Tama Nagayama Hospital. As anonymous data were analysed, the requirement for informed consent was waived.

Settings
The basic policies of the Ministry of Health, Labour, and Welfare of Japan for the treatment of COVID-19 patients are as follows: all patients with a positive SARS-CoV-2 test result, diagnosed with COVID-19 are admitted to the hospital, while some asymptomatic COVID-19 patients or COVID-19 patients who do not require medical care are isolated either at home or at a designated hotel.

The health system in Japan ensures that the quality of medication use is homogenized, owing to the Japanese universal health insurance coverage system. The insurance system warrants a health check-up at any hospital of the patient’s choice, and that the patients are transported to the nearest hospital in an ambulance. All patients fundamentally receive the same healthcare services provided by the health insurance system in all hospitals, although the medical staff decide the treatment strategy considering the patients’ age, activity of daily living, medical history, and patients’ or their family’s intentions when the patients are critically ill and require intensive care.

Study design
We conducted an observational cohort study using the COVID-19 Registry Japan (COVIREGI-JP) database, a nationwide, multi-centre database created by the National Centre for Global Health and Medicine [14]. The COVIREGI-JP database contains data of hospitalized patients with laboratory-confirmed COVID-19 who were admitted after 1 January 2020, from 925 participating hospitals throughout Japan. These records include information about the patients’ age, sex, body mass index (BMI), comorbidities, cause of infection, symptoms, vital signs on admission day, vital signs during hospitalization, treatments, results of laboratory tests, drugs, complications, and outcome at discharge. The follow-up ends at the patients’ discharge or death. The study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based data capture application hosted at the Joint Centre for Researchers, Associates, and Clinicians data centre of the National Centre for Global Health and Medicine. Data from the COVIREGI-JP database, of the National Centre for Global Health and Medicine, were used for this study with permission.

Participants
The present study included all COVID-19 patients who were admitted to a hospital and required IMV and were registered in the COVIREGI-JP database from 1 January 2020 to 28 February 2021.

Outcome measures
The primary outcome was all-cause in-hospital mortality. The secondary outcomes were complications during hospitalization, tracheostomy at discharge, and oxygen therapy at discharge. Complications included bacterial pneumonia, acute respiratory distress syndrome (ARDS), meningitis, ventricular fibrillation, deep venous thrombosis, and pulmonary embolism.

Definition
We considered the specified time course because the spread and treatment strategy for COVID-19 have been changing drastically over time. Accordingly, we classified the study duration into three periods, in accordance with the epidemic trends of COVID-19 in Japan: the first wave from 1 January 2020 to 31 May 2020, the second wave from 1 June 2020 to 30 September 2020, and the third wave occurred after 1 October 2020.

The actual diagnosis of ARDS was made by each participating doctor in charge in the clinical setting based on the Berlin definition 2012 [15], and the definitions of some variables using logistic regression analysis
(comorbidity, immunosuppression, drug administration for COVID-19, and drug administration for coagulopathy) are shown in Additional file 1: Table S1.

**Statistical analysis**

We stratified the records into 10 each by age group (in 10-year increments). Continuous values were expressed as mean (standard deviation), and categorical values were expressed as numbers (%). Since this was an observational study, values were compared using standardized difference [16]. Next, we contrasted survivors with non-survivors in the study group based on the characteristics, treatments, medications, and complications. Further, we performed multiple imputation to decrease the bias caused by incomplete data; each missing value was replaced with a set of five substitute plausible values [17, 18]. Models were constructed for each imputed dataset, and a single model was created by statistical inference with the results of the five imputed datasets. We performed multiple imputations of covariates via fully conditional specification, including all variables listed in Table 4 and outcomes. Then, we evaluated mortality between age groups using a multivariable regression analysis after adjusting for known potential components and for within-hospital clustering using generalized estimation equation. Treatments and patient care vary between hospitals, even though treatment guidelines for COVID-19 are followed [19, 20]. Therefore, we considered clustering effect within hospital groups. We selected variables independently associated with COVID-19 mortality for logistic regression analysis, referring to previous studies for clinically important factors [21, 22], and the variables were as follows: sex, steroid use, drug administration for COVID-19, the admission date, BMI (< 30 kg/m², ≥ 30 kg/m²), fever (< 38 °C, ≥ 38 °C), SpO2 < 90%, respiratory rate ≥ 30, Systolic blood pressure ≤ 80 mmHg, comorbidities, immunosuppression status, medication use for coagulopathy, ARDS, and days from symptom onset to IMV [4, 7, 8, 10–13, 23].

Statistical significance was set at \( p < 0.05 \). All data were analysed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

**Results**

**Patient characteristics, vital signs, and symptoms at admission**

Of the data obtained from 33,808 cases, the final study population was 1555 (Fig. 1). The mean (standard deviation) age was 64.3 years (12.3) in the survivor group and 73.4 years (9.9) in the non-survivor group. There were 904 (80.3%) males in the survivor group and 306 (76.3%) in the non-survivor group.

The number of patients who had comorbidities and were immunosuppressed was 842 (74.6%) and 32 (2.9%), respectively, in the survivor group, and 336 (83.8%) and 23 (6.0%), respectively, in the non-survivor group. Fever (over 38 °C at admission) was reported in 369 (32.9%) patients in the survivor group and 110
| Variables | Survivor ($n = 1128$) | Non-survivor ($n = 401$) | Standardized difference, % |
|-----------|-----------------------|--------------------------|-----------------------------|
| Age, years | 64.3 (12.3)           | 73.4 (9.9)               | - 81.5                      |
| Male      | 904/1126 (80.3)       | 306/401 (76.3)           | 9.72                        |
| Body mass index $\geq 30$ | 157/940 (16.7) | 40/314 (12.7) | 11.31 |
| Admission date | | | | |
| 3rd wave (October 1st--) | 484/1126 (43.0) | 175/401 (43.6) | - 1.21 |
| 2nd wave (June 1st, 2020–September 30, 2020) | 258/1126 (22.9) | 71/401 (17.7) | 12.95 |
| 1st wave (January 26, 2020–May 31, 2020) | 384/1126 (34.1) | 155/401 (38.7) | - 9.57 |
| Race | | | | |
| Japanese | 1091/1120 (97.4) | 391/395 (99.0) | - 12.06 |
| Smoking history | 527/866 (60.9) | 177/288 (61.5) | - 1.23 |
| Drinking history | 432/709 (60.9) | 121/229 (52.8) | 16.41 |
| Comorbidity | 842/1128 (74.6) | 336/401 (83.8) | - 22.81 |
| Hypertension | 552/1128 (48.9) | 193/401 (48.1) | 1.60 |
| Diabetes | 389/1128 (34.5) | 158/401 (39.4) | - 10.16 |
| Hyperlipidemia | 256/1128 (22.7) | 97/401 (24.2) | - 3.54 |
| Cerebrovascular disease | 97/1128 (8.6) | 54/401 (13.5) | 15.68 |
| COPD | 71/1128 (6.3) | 30/401 (7.5) | - 4.74 |
| Bronchial asthma | 63/1128 (5.6) | 19/401 (4.7) | 4.07 |
| Solid tumor | 50/1128 (4.4) | 32/401 (8.0) | - 14.97 |
| Liver disease | 46/1126 (4.1) | 22/401 (5.5) | - 6.55 |
| Moderate-to-severe chronic kidney disease | 41/1128 (3.6) | 29/401 (7.2) | - 15.98 |
| Ischemic heart disease | 41/1128 (3.6) | 26/401 (6.5) | - 13.27 |
| Congestive heart failure | 35/1128 (3.1) | 25/401 (6.2) | - 14.76 |
| Major neurocognitive disorder | 28/1128 (2.5) | 28/401 (8.3) | - 25.88 |
| Chronic lung disease excluding COPD | 28/1128 (2.5) | 26/401 (6.5) | - 19.39 |
| Hemodialysis before admission | 28/1128 (3.1) | 22/401 (5.5) | - 11.85 |
| Collagen disease | 19/1128 (1.7) | 11/401 (2.7) | - 6.82 |
| Metastatic solid tumor | 7/1128 (0.6) | 7/401 (1.7) | - 10.33 |
| Lymphoma | 7/1128 (0.6) | 5/401 (1.2) | - 6.36 |
| Leukemia | 0/1128 (0) | 2/401 (0.5) | - 10.33 |
| Immunosuppression | 32/1091 (2.9) | 23/384 (6.0) | 0.01 |
| Vital signs on admission | | | | |
| AVPU scale A (Alert) | 846/1021 (82.8) | 281/366 (76.8) | 14.99 |
| Fever (≥ 38 °C) | 369/1121 (32.9) | 110/397 (27.7) | 11.33 |
| Respiratory rate ≥ 30 breaths/minute | 168/1011 (16.6) | 61/359 (17.0) | - 1.07 |
| SpO2 < 90% | 163/1114 (14.1) | 71/391 (18.2) | - 8.33 |
| Systolic blood pressure ≤ 80 mmHg | 20/1112 (1.8) | 3/396 (0.8) | 8.84 |
| Symptoms at admission | 1088/1102 (98.7) | 378/387 (97.7) | 7.53 |

Analysis based on records from the COVID-19 Registry Japan. Data given as number of positive observations/total number of observations (percentage) or as mean (standard deviation). For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each phase and the total number of observations

COPD: chronic obstructive pulmonary disease, SD: standardized difference. IMV: invasive mechanical ventilation

For continuous variables, the standardized difference ($d$) is defined as follows:

$$d = \sqrt{\frac{\text{survivor} - \text{non-survivor}}{\text{survivor} + \text{non-survivor}} \times \left(\frac{\text{survivor} + \text{non-survivor}}{2}\right)^2}$$

For dichotomous variables, the standardized difference is defined as follows:

$$d = \sqrt{\frac{\text{survivor} - \text{non-survivor}}{\text{survivor} + \text{non-survivor}} \times \left(\frac{\text{survivor} + \text{non-survivor}}{2}\right)^2}$$

$\bar{x}$: mean, $s$: standard deviation, $\hat{p}$: proportion
(27.7%) in the non-survivor group. SpO₂ under 90% at admission was observed in 163 (15.1%) patients in the survivor group and 71 (18.2%) in the non-survivor group. The number of patients with symptoms at admission was 1,088 (98.7%) in the survivor group and 378 (97.7%) in the non-survivor group (Table 1). More than 10% of the data were missing for BMI, smoking history, drinking history, and complication of deep vein thrombosis (Table 1).

**Mortality by age group**

The in-hospital mortality rate was 26.3% (401/1529). When assessed by the age groups, the mortality rate was 8.6% (24/278), 20.7% (80/387), 34.9% (177/507), 49.7% (99/199), and 83.3% (10/12) for patients in their 50 s, 60 s, 70 s, 80 s, and 90 s, respectively (Fig. 2).

**Treatments and complications**

The mean (standard deviation) number of days from symptom onset to IMV therapy was 8.8 days (13.3) for patients who survived and 17.4 days (24.1) for those who died. The percentage of patients who were administered medication for COVID-19 was 89.8% (1008/1122) among survivors and 89.1% (353/396) among non-survivors; 69.6% (767/1102) and 72.2% (286/396) were administered steroids among survivors and non-survivors, respectively (Table 2). The prevalence of severe ARDS was 20.4% (212/1039) in the survivor group and 63.3% (217/343) in the non-survivor group. The number of patients who underwent tracheotomy and oxygen therapy at discharge were 116 (10.3%) and 563 (49.9%), respectively (Table 3).

**Multivariable analysis for risk of in-hospital mortality**

The multivariable analysis showed that a 10-year increase in age was significantly associated with mortality (Table 4). The odds ratio of death was 7 times higher in patients in their 70s (OR, 6.92; 95% confidence interval [CI] 4.23 to 11.31; p < 0.01), 13 times higher in patients in their 80s (OR, 13.17; 95% CI 7.21 to 24.06; p < 0.01), and 92 times higher in patients in their 90s (OR, 92.63; 95% CI 16.66 to 514.98; p < 0.01), compared with those aged < 60 years.
Severe ARDS was associated with high mortality rates (OR, 6.73; 95% CI 4.50 to 10.04; \( p < 0.01 \)); however, moderate ARDS and mild ARDS were not related to mortality (OR, 0.63; 95% CI 0.39 to 1.02; \( p = 0.06 \), OR, 0.54; 95% CI 0.23 to 1.28; \( p = 0.16 \)).

Table 2  Treatments of patients with coronavirus disease 2019 under invasive mechanical ventilation therapy

| Variables                                | Survivor  | Non-survivor  | Standardized difference, % |
|------------------------------------------|-----------|--------------|----------------------------|
| Drug administration for COVID-19         | 1008/1122 | 353/396      | 2.28                       |
| Favipiravir                               | 545/993   | 200/349      | -4.84                      |
| Remdesivir                                | 437/987   | 127/347      | 15.74                      |
| Ciclesonide                               | 231/991   | 73/347       | 5.54                       |
| Nafamostat                                | 156/964   | 66/337       | -8.88                      |
| Tocilizumab                               | 123/964   | 37/337       | 5.56                       |
| Hydroxychloroquine                        | 56/991    | 26/348       | -7.25                      |
| Lopinavir and ritonavir                   | 50/991    | 23/347       | -6.85                      |
| Ivermectin                                | 7/977     | 2/344        | 1.24                       |
| Interferon                                | 3/1007    | 2/355        | -4.48                      |
| Baricitinib                               | 0/978     | 1/344        | -7.76                      |
| Antibiotics                               | 832/1103  | 336/393      | 25.68                      |
| Antifungal agent                          | 60/1105   | 60/390       | -33.21                     |
| Neuraminidase inhibitor                   | 12/1099   | 10/389       | -11.15                     |
| Steroid (excluding ciclesonide)           | 767/1102  | 286/396      | -5.73                      |
| Drug administration for coagulopathy      | 695/1066  | 252/376      | -3.80                      |
| Anticoagulant agents                      | 655/1126  | 239/401      | 2.85                       |
| Antiplatelet agents                       | 109/1066  | 47/376       | -7.56                      |
| Thrombolytic agents                       | 12/1068   | 5/376        | 1.84                       |
| Plasmapheresis                            | 8/1124    | 6/399        | -7.68                      |
| Immunoglobulin                            | 57/1124   | 43/397       | -21.19                     |
| Vasopressor/inotrope support              | 430/1116  | 259/395      | -56.36                     |
| Renal replacement therapy                 | 93/1117   | 120/399      | -57.60                     |
| Prone positioning                         | 344/1109  | 142/397      | -10.19                     |
| High-flow oxygen device use               | 222/1120  | 88/398       | -5.65                      |
| Noninvasive positive pressure ventilation  | 147/1124  | 42/398       | 7.74                       |
| Duration of symptom onset to IMV, days    | 8.8 (13.3)| 8.7 (6.2)    | 0.96                       |
| Duration of IMV, days                     | 10.6 (13.3)| 17.4 (24.1) | -34.9                      |
| Re-intubation                             | 43/1094   | 26/396       | -12.13                     |
| Nitric oxide inhalation                   | 17/1118   | 12/399       | -10.13                     |
| Neuromuscular blocking agent              | 56/1067   | 184/374      | 6.81                       |
| Tracheotomy                               | 172/1119  | 84/399       | -14.80                     |
| Extracorporeal membrane oxygenation       | 106/1127  | 45/401       | -5.92                      |

Analysis based on records from the COVID-19 Registry Japan. Data given as number of positive observations/total number of observations (percentage) or as mean (standard deviation). For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each phase and the total number of observations.

IMV: invasive mechanical ventilation, SD: standardized difference

For continuous variables, the standardized difference (\( d \)) is defined as follows:

\[
d = \left( \frac{\bar{x}_{\text{survivor}} - \bar{x}_{\text{non-survivor}}}{s} \right) \sqrt{\frac{n_{\text{survivor}} + n_{\text{non-survivor}}}{n_{\text{survivor}} + n_{\text{non-survivor}}}}
\]

For dichotomous variables, the standardized difference is defined as follows:

\[
d = \left( \frac{p_{\text{survivor}} - p_{\text{non-survivor}}}{s} \right) \sqrt{\frac{p_{\text{survivor}}(1 - p_{\text{survivor}}) + p_{\text{non-survivor}}(1 - p_{\text{non-survivor}})}{n_{\text{survivor}} + n_{\text{non-survivor}}}}
\]

\( \bar{x} \): mean, \( s \): standard deviation, \( p \): proportion

Discussion

This nationwide cohort study assessed the relationship between mortality from COVID-19 and IMV, stratified by age. This study found that mortality drastically increased with increasing age among patients who required mechanical ventilation support.
The current study precisely reported mortality in COVID-19 patients who underwent IMV, which is the most critically ill group, in a large population. Although some studies have reported findings on critically ill patients with COVID-19, only a few large-sample surveys have focused on patients undergoing IMV, which is one of the most important treatment options for pneumonia and respiratory illness [4–7, 11, 12]. Therefore, this study may be valuable in understanding the epidemiology of severe respiratory dysfunction caused by COVID-19.

The results of our study demonstrated that increasing age was firmly associated with a higher risk of mortality in COVID-19 patients undergoing IMV. Although previous studies have reported the risk of advanced age, the current study suggested that age was associated with a higher risk in comparison to other factors, and that preventing progression to severe COVID-19 in elderly patients may be a great public health issue. Vaccination, careful observation for asymptomatic patients with COVID-19, and early treatment for symptomatic patients with COVID-19 may be strongly recommended for the people aged > 60 years.

This study also indicated other features of severe COVID-19. The definition of ARDS as a COVID-19 complication adopted in this study was based on the Berlin definition 2012; respiratory failure occurred within 1 week of known clinical insult or new or worsening respiratory symptoms (Additional file 1: Table S1) [15]. ARDS was not diagnosed in 44.3% of survivors and 25.7% of non-survivors, and the mean duration from symptom onset to IMV therapy was about 9 days in both groups. These results suggested that several patients struggling

### Table 3  Outcomes of patients with coronavirus disease 2019 under invasive mechanical ventilation therapy

| Variables                          | Survivor (n = 1128) | Non-survivor (n = 401) | Standardized difference, % |
|-----------------------------------|--------------------|------------------------|----------------------------|
| Complications                     |                    |                        |                            |
| Viral pneumonia (excluding COVID-19) | 39/1057 (3.5)      | 24/358 (6.7)           | − 14.58                    |
| Bacterial pneumonia               | 290/1051 (27.6)    | 180/360 (50.0)         | − 47.23                    |
| Acute respiratory distress syndrome|                    |                        |                            |
| None                              | 460/1039 (44.3)    | 88/343 (25.7)          | 39.76                      |
| Mild                              | 85/1039 (8.2)      | 6/343 (1.7)            | 30.31                      |
| Moderate                          | 282/1039 (27.1)    | 32/343 (9.3)           | 47.41                      |
| Severe                            | 212/1039 (20.4)    | 217/343 (63.3)         | − 96.57                    |
| Pleural effusion                  | 144/1082 (13.3)    | 98/371 (26.4)          | − 33.29                    |
| Bacteremia                        | 79/1093 (7.2)      | 71/371 (19.1)          | − 35.77                    |
| Deep vein thrombosis              | 61/995 (6.1)       | 19/326 (5.8)           | 1.27                       |
| Pneumothorax                      | 33/1093 (3.0)      | 51/380 (13.4)          | − 38.61                    |
| Hemoptysis                        | 31/1050 (3.0)      | 34/361 (9.4)           | − 26.78                    |
| Ventricular defibrillation, ventricular tachycardia | 28/1097 (2.6) | 30/376 (8.0) | − 24.28                     |
| Gastrointestinal bleeding         | 23/1094 (2.1)      | 46/379 (12.1)          | − 39.70                    |
| Seizures                          | 21/1101 (1.9)      | 5/381 (1.3)            | 4.78                       |
| Cerebral infarction, cerebral hemorrhage | 20/1104 (1.8) | 21/372 (5.6)        | − 20.23                    |
| Pulmonary embolism                | 20/1022 (2.0)      | 14/335 (4.2)           | − 12.72                    |
| Ischemic heart disease            | 18/1098 (1.6)      | 8/374 (2.1)            | − 3.71                     |
| Myocarditis, pericarditis, cardiomyopathy | 10/1100 (0.9) | 4/373 (1.1)       | − 2.01                     |
| Meningitis, encephalitis          | 7/1075 (0.7)       | 2/363 (0.6)            | 1.24                       |
| Endocarditis                      | 4/1065 (0.4)       | 1/359 (0.3)            | 1.69                       |
| Tracheotomy at discharge          | 116/1128 (10.3)    |                        |                            |
| Oxygen therapy at discharge       | 563/1128 (49.9)    |                        |                            |

Analysis based on records from the COVID-19 Registry Japan. Data given as number of positive observations/total number of observations (percentage). For each variable, the number of missing observations can be obtained as the difference between the total number of patients in each phase and the total number of observations.

For continuous variables, the standardized difference \( d \) is defined as follows:

\[
d = \frac{(\mu_{\text{survivor}} - \mu_{\text{non-survivor}})}{\sqrt{(s_{\text{survivor}}^2 + s_{\text{non-survivor}}^2)/2}}
\]

For dichotomous variables, the standardized difference is defined as follows:

\[
d = \frac{\hat{p}_{\text{survivor}} - \hat{p}_{\text{non-survivor}}}{\sqrt{\left\{(\hat{p}_{\text{survivor}}(1 - \hat{p}_{\text{survivor}}) + \hat{p}_{\text{non-survivor}}(1 - \hat{p}_{\text{non-survivor}})\right\}/2}}
\]

\( \mu \): mean, \( s \): standard deviation, \( \hat{p} \): proportion
with severe COVID-19 showed gradual deterioration over a 1-week period, and required IMV therapy. However, multivariable analysis showed that severe ARDS was associated with high risk of mortality; that is, acute deterioration in COVID-19 patients might be a sign of worse outcome.

The strength of this study is its design, as it is a nationwide, multi-centre survey in Japan. Initially, we demonstrated some features of the Japanese medical system. As the Japanese health insurance system supports homogenizing and generalizing the Japanese medical system, the outcome of this study was the result of uniformed standard medical treatment, including IMV support, for all ages. In the present Japanese super-aging society, our study revealed that older age had a great effect on mortality associated with IMV therapy in COVID-19 patients, after adjusting for important variables that are independently associated with mortality. This result may be helpful in developing effective therapeutic strategies against COVID-19.

There are some limitations to the current study. First, Dawn et al., reported that high demand for the intensive care unit services and workload have an effect on mortality [24], and a similar situation was observed in Japan during the study period. In addition, the size of the hospitals that participated in the current study varied. Second, this database did not include information about the strain of COVID-19; therefore, we could not adjust for the effect of the COVID-19 strain on mortality. To reduce the effect of these two factors, we adjusted for hospital clustering and time course. Third, these results may not be generalizable to other countries where the medical and social systems are different from those in Japan. Fourth, the occurrence of the primary outcome might influence/preclude the occurrence of secondary outcomes (complications, tracheostomy, or oxygen therapy at discharge). However, we could not evaluate the cause of death in the current study. Thus, we could not evaluate the cause–effect relationship between the primary and secondary outcomes. Finally, the diagnosis of complications was made by each doctor in charge in the clinical setting. There might be a possibility of misdiagnosis because of these factors.

**Conclusion**

The findings of this multi-centre, observational study, which assessed COVID-19 patients in Japan, demonstrated that age was a crucial prognostic factor in identifying patients at risk of dying among critically ill COVID-19 patients who required IMV. Further large-scale, prospective studies are required to validate our results.

**Abbreviations**

COVID-19: Coronavirus disease 2019; IMV: Invasive mechanical ventilation; ARDS: Acute respiratory distress syndrome; BMI: Body mass index; COVIREGI-JP: COVID-19 Registry Japan; CI: Confidence interval.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13613-021-00959-6.

**Additional file 1: Table S1.** Definition of the variables for confounding factors using multivariable analysis in Table 4.

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**Table 4** Multiple logistic regression analysis of in-hospital mortality risk among coronavirus disease 2019 patients on mechanical ventilation after adjusting for within-hospital clustering

| Variable                                      | After multiple imputation | Odds ratio  | 95% CI         | p-value |
|-----------------------------------------------|----------------------------|-------------|----------------|---------|
| Age ≥ 90                                      |                            | 92.63       | 16.66–514.98   | <0.01   |
| 80–89                                         |                            | 13.17       | 7.21–24.06     | <0.01   |
| 70–79                                         |                            | 6.92        | 4.23–11.31     | <0.01   |
| 60–69                                         |                            | 2.60        | 1.65–4.08      | <0.01   |
| 59 ≤ (reference)                              |                            | 1           |                |         |
| Male                                          |                            | 1.04        | 0.74–1.46      | 0.82    |
| Body mass index ≥ 30 kg/m²                     |                            | 1.37        | 0.91–2.07      | 0.14    |
| Smoking history                               |                            | 1.16        | 0.80–1.68      | 0.44    |
| Comorbidity                                   |                            | 1.33        | 0.87–2.03      | 0.19    |
| Immunosuppression                             |                            | 2.17        | 1.14–4.12      | 0.02    |
| Admission date                                |                            | 0.86        | 0.59–1.26      | 0.45    |
| Vital signs on admission                      |                            | 0.62        | 0.41–0.95      | 0.03    |
| Fever (≥ 38 °C)                                |                            | 0.83        | 0.61–1.13      | 0.25    |
| SpO2 < 90%                                     |                            | 1.00        | 0.68–1.46      | 0.99    |
| Respiratory rate ≥ 30                          |                            | 1.02        | 0.70–1.50      | 0.90    |
| Systolic blood pressure ≤ 80 mmHg             |                            | 0.25        | 0.07–0.96      | 0.04    |
| ARDS                                          |                            |             |                |         |
| Severe                                        |                            | 6.73        | 4.50–10.04     | <0.01   |
| Moderate                                      |                            | 0.63        | 0.39–1.02      | 0.06    |
| Mild                                          |                            | 0.54        | 0.23–1.28      | 0.16    |
| None (reference)                              |                            | 1           |                |         |
| Drug administration for COVID-19              |                            | 0.97        | 0.56–1.67      | 0.90    |
| Steroid use                                   |                            | 1.26        | 0.84–1.88      | 0.26    |
| Drug administration for coagulopathy          |                            | 0.96        | 0.68–1.35      | 0.82    |
| Days from symptom onset to IMV                |                            | 1.00        | 1.00–1.01      | 0.47    |

Analysis based on records from the COVID-19 Registry Japan
ARDs acute respiratory distress syndrome, IMV invasive mechanical ventilation
Acknowledgements
Not applicable.

Authors’ contributions
All authors contributed to the write-up of this manuscript. CT analysed the data and contributed to writing of the manuscript. TT oversaw the analysis and interpretation. FN, SK, AT, JK, YI, SS, AS, MK and KU were responsible for the data interpretation. MH, TM, YA and NO performed the data collection. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The ethics committee of the Nippon Medical School Tama Nagayama Hospital approved this study. Written informed consent was waived because our analysis did not include personal identifying information.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 9 August 2021   Accepted: 22 November 2021
Published online: 11 December 2021

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