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The characteristics and clinical course of patients with COVID-19 who received invasive mechanical ventilation in Osaka, Japan

Atsushi Hirayama[a,b,*,1], Jun Masui[a,1], Ayumi Murayama[a], Satomi Fujita[a], Jun Okamoto[a], Jun Tanaka[a], Takanori Hirayama[a], Toshitake Ohara[a], Emma Nakagawa Hoffmann[a,b], Jingwen Zhang[a,b], Haruna Kawachi[a,b], Hideo Okuno[c], Shigeto Hamaguchi[c], Kazunori Tomono[c], Rumiko Asada[a]

[a] Osaka Prefectural Government, Osaka, Japan
[b] Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[c] Division of Infection Control and Prevention, Osaka University Hospital, Osaka, Japan

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ABSTRACT

Objective: To describe the detailed clinical course of patients with coronavirus disease 2019 (COVID-19) who received invasive mechanical ventilation.
Methods: We conducted a case series of patients with COVID-19 who received invasive mechanical ventilation in Osaka, Japan, between January 29 and May 28, 2020. We describe the patient characteristics and clinical course from onset. Additionally, we fitted logistic regression models to investigate the associations between patient characteristics and the 30-day mortality rate.
Results: A total of 125 patients who received invasive mechanical ventilation (median age [interquartile range], 68 [57–73] years; male, 77.6%) were enrolled. Overall, the 30-day mortality was 24.0%, and the median (interquartile range) length of ICU stay and length of invasive mechanical ventilation use were 16 (12–29) days and 13 (9–26) days, respectively. From clinical onset, 121 patients (96.8%) were intubated within 14 days. In multivariable logistic regression analysis, age of 65 years or older (odds ratio, 3.56; 95% confidence interval, 1.21–10.49; $P = 0.02$) and male sex (odds ratio, 3.75; 95% confidence interval, 1.00–11.24, $P = 0.04$) were significantly associated with a higher 30-day mortality rate.
Conclusions: In this case series of patients with COVID-19 who received invasive mechanical ventilation in Japan, the 30-day mortality rate was 24.0%, and age 65 years or older and male sex were associated with higher 30-day mortality rate.

Introduction

In Japan, the first laboratory-confirmed case of coronavirus disease 2019 (COVID-19) was detected on January 16, 2020. Subsequently, the first case in Osaka was detected on January 29, 2020. On April 7, 2020, in response to the rapid spread of COVID-19, the Japanese government declared a state of emergency (Ministry of Health, Labour and Welfare of Japan, 2020a). Early studies showed that 2–12% of patients required invasive mechanical ventilation, and the mortality rate of these patients was 26–97% (Zhou et al., 2020; Hu et al., 2020; Richardson et al., 2020; Yang et al., 2020; Grasselli et al., 2020). However, detailed information such as 30-day mortality rate, time from clinical onset to intubation, or length of ICU stay for patients with laboratory-confirmed COVID-19 who required invasive mechanical ventilation in the earlier phase of the COVID-19 outbreak in Japan is scarce.

* Corresponding author at: Osaka Prefectural Government, 2, Otemae, Chuo-ku, Osaka 540-8570, Japan.
E-mail addresses: ath877@mail.harvard.edu (A. Hirayama), masuiju@mbox.pref.osaka.lg.jp (J. Masui), murayamaa@mbox.pref.osaka.lg.jp (A. Murayama), fujitassa@mbox.pref.osaka.lg.jp (S. Fujita), m04013jo@m.u-tokyo.ac.jp (J. Okamoto), TanakaJ0925@mbox.pref.osaka.lg.jp (J. Tanaka), hirayamata@mbox.pref.osaka.lg.jp (T. Hirayama), oharatos@mbox.pref.osaka.lg.jp (T. Ohara), nakagawaema@pbox.pref.osaka.lg.jp (E.N. Hoffmann), chiyoj@rbox.pref.osaka.lg.jp (J. Zhang), kawachih@pbox.pref.osaka.lg.jp (H. Kawachi), okuno-h@niid.go.jp (H. Okuno), hamaguchi.shigeto@gmail.com (S. Hamaguchi), tomono@hp-infect.med.osaka-u.ac.jp (K. Tomono), asadar@mbox.pref.osaka.lg.jp (R. Asada).
[1] AH and JM contributed equally to this work.

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Table 1
Clinical course and outcome of patients with laboratory-confirmed coronavirus disease 2019 (COVID-19) who required mechanical ventilation by age.

	All n = 125	<50 years n = 16	50–64 years n = 33	65–74 years n = 45	≥75 years n = 31	P
Median time (IQR) from clinical onset to intubation[a], days	8 (6–10)	7 (5–8)	9 (7–11)	8 (5–11)	8 (6–10)	0.72
ECMO use, n (%)	20 (16.0)	4 (25.0)	7 (21.2)	8 (17.8)	1 (3.2)	0.14
Renal replacement therapy use, n (%)	22 (17.6)	2 (12.5)	1 (3.0)	10 (22.2)	9 (29.0)	0.02
Median length (IQR) of ICU stay, days	16 (12–29)	14 (6–19)	12 (11–19)	22 (12–36)	17 (12–34)	0.01
Median length (IQR) of invasive mechanical ventilation use, days	13 (9–26)	10 (6–13)	11 (8–16)	16 (11–36)	20 (10–28)	0.01
Median length (IQR) of ECMO use, days	11 (9–16)	13 (10–15)	9 (4–15)	13 (10–27)	11 (NA)	0.44
Median duration (IQR) of viral RNA shedding from clinical onset[b], days	35 (29–41)	34 (30–42)	33 (29–38)	35 (27–41)	43 (39–47)	0.13
Died within 30 days, n (%)	30 (24.0)	2 (12.5)	4 (12.1)	10 (22.2)	14 (45.2)	0.01
Still treated in the ICU at 30 days from ICU hospitalization, n (%)	28 (22.4)	1 (6.3)	3 (9.1)	15 (33.3)	9 (29.0)	0.02
Discharged alive from the ICU, n, %	67 (53.6)	13 (81.2)	26 (78.8)	20 (44.4)	8 (25.8)	<0.001

Continuous variables are shown as the median and interquartile range (IQR), and categorical variables are shown in the number and percentage. The Kruskal–Wallis test and Fisher's exact test were used to compare the variables across age groups.
ECMO, extracorporeal membrane oxygenation; NA, not available.
[a] Information missing on date of clinical onset for four patients.
[b] Information missing on date of clinical onset for four patients and on date of viral RNA shedding for 57 patients.

Methods

We conducted a retrospective observational study using data from an active epidemiological investigation into COVID-19 that was conducted under the Infectious Diseases Control Law (National Institute of Infectious Diseases, 2020). According to the Guidelines for Epidemiological Studies established by the Ministry of Health, Labour and Welfare of Japan, this study did not require approval from an ethics committee (Ministry of Health, Labour and Welfare of Japan, 2020b). The detailed methods of the present study are described in Supplemental Methods. We identified all consecutive hospitalized patients with laboratory-confirmed COVID-19 who received invasive mechanical ventilation in Osaka from January 29 to April 28, 2020, and the last follow-up date was May 28, 2020. The primary outcome of this study was the mortality rate 30 days after ICU hospitalization. We categorized age into four groups: less than 50 years, 50–64 years, 65–74 years, and 75 years or more. The Kruskal–Wallis test and Fisher's exact test were used to compare the variables across age categories. Univariable and multivariable logistic regression analyses were used to investigate the association between patient characteristics and 30-day mortality rate. All P values were two-tailed, with $P < 0.05$ considered statistically significant. All statistical analyses were performed with Stata/MP version 16.0 (StataCorp, Lakeway Drive, College Station, TX, USA).

Table 2
Patient characteristics and 30-day mortality rate among patients with laboratory-confirmed coronavirus disease 2019 (COVID-19) who required mechanical ventilation.

	30-day mortality rate (%)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Aged ≥65 years vs. aged <65 years	31.6 (24/76) vs. 12.2 (6/49)	3.31 (1.24–8.83)	0.02	3.56 (1.21–10.49)	0.02
Men vs. women	26.8 (26/97) vs. 14.3 (4/28)	2.20 (0.70–6.94)	0.18	3.75 (1.00–11.24)	0.04
Current/past smoker vs. never smoked	23.5 (12/51) vs. (25.6 (11/43)	0.90 (0.35–2.30)	0.92	0.56 (0.19–1.67)	0.30
Comorbidities					
Cancer vs. without cancer	54.6 (6/11) vs. 21.1 (24/114)	4.50 (1.26–16.01)	0.02	–	–
Cardiovascular disease vs. without cardiovascular disease	50 (8/16) vs. 20.2 (22/109)	3.95 (1.34–11.71)	0.01	–	–
Diabetes vs. without diabetes	37.2 (16/43) vs. 17.1 (14/82)	2.88 (1.24–6.70)	0.01	–	–
Diabetes with insulin use vs. diabetes without insulin use	50 (1/2) vs. 36.6 (15/41)	1.73 (0.11–29.78)	0.71	–	–
Hypertension vs. without hypertension	17.2 (5/29) vs. 26.0 (25/96)	0.59 (0.20–1.72)	0.34	–	–
Immunodeficiency/immunosuppressant use vs. without immunodeficiency/immunosuppressant	14.3 (1/7) vs. 24.6 (29/118)	0.51 (0.06–4.43)	0.54	–	–
Maintenance dialysis vs. without maintenance dialysis	50 (1/2) vs. 23.6 (29/123)	3.24 (0.20–53.46)	0.41	–	–
Mental disorder vs. without mental disorder	100 (1/1) vs. 23.4 (29/124)	NA	NA	–	–
Respiratory disease vs. without respiratory disease	26.7 (4/15) vs. 23.6 (26/110)	1.17 (0.34–4.00)	0.80	–	–
No. of comorbidities ≥1 vs. no comorbidity	30.3 (23/76) vs. 14.3 (7/49)	2.60 (1.02–6.65)	0.04	2.56 (0.91–7.21)	0.08
ECMO use vs. without ECMO use	25 (5/20) vs. 23.8 (25/105)	1.07 (0.35–3.23)	0.91	0.85 (0.24–3.30)	0.80
Renal replacement therapy use vs. without renal replacement therapy use	40.9 (9/22) vs. 20.4 (21/103)	2.70 (1.02–7.12)	0.04	1.47 (0.49–4.36)	0.49

Odds ratios (ORs) were calculated by unadjusted and adjusted logistic regression analysis.
CI, confidence interval; ECMO, extracorporeal membrane oxygenation; NA, not available.

Results

As of April 28, 2020, a cumulative total of 1553 patients with laboratory-confirmed COVID-19 were identified in Osaka, Japan. Of these, 125 patients (8.1%) hospitalized in 18 hospitals received invasive mechanical ventilation. Overall, the median age (interquartile range) was 68 (57–73) years, and 97 patients (77.6%) were male. Of these, 30 (24.0%) died within 30 days from ICU hospitalization. Renal replacement therapy use, length of ICU stay, length of invasive mechanical ventilation, and 30-day mortality rate differed across age groups (all $P < 0.05$; Table 1). A total of 121 patients (96.8%) were intubated within 14 days from clinical onset (Supplemental Figure 1). In multivariable logistic regression analysis, age 65 years or older (odds ratio, 3.56; 95% confidence interval, 1.21 10.49; $P = 0.02$) and male sex (odds ratio, 3.75; 95% confidence interval, 1.00–11.24, $P = 0.04$) were significantly associated with a higher 30-day mortality rate (Table 2).

Discussion

Although the follow-up periods varied in each study, the mortality rates of mechanically ventilated COVID-19 patients differed across countries in the early stage of the COVID-19 pandemic. Early studies reported from other countries revealed that 26–97% of patients who received invasive mechanical ventilation died (Zhou et al., 2020; Richardson et al., 2020; Yang et al., 2020; Grasselli et al., 2020). These reported higher mortality rates were reflective of the different thresholds put in place for hospitalization by each country during the early stages of the outbreak. Although Japan also suffered from significant disarray during the study period, medical resources were strategically sourced in time to prevent severe disruption of the healthcare system in Osaka. We found the median time from clinical onset to intubation was 8 days, and 97% of patients were intubated within 14 days from clinical onset. In a case series of 21 critically ill patients in the USA, the mean time from clinical onset to hospitalization was 3.5 days, and 81% of those patients were admitted to the ICU less than 24 h after hospitalization (Arentz et al., 2020). A retrospective single-center study from Shanghai revealed that 22 patients treated in the ICU were admitted 8.5 ± 4.0 days from clinical onset (Chen et al., 2020). These findings support our clinical implication that patients with laboratory-confirmed COVID-19 should be carefully observed for at least 14 days from clinical onset regardless of their symptoms.

Our study has several potential limitations. First, because the data were analyzed as of May 28, 2020, 22.4% of patients (28 of 125) were still being treated in the ICU. Second, we did not set a common treatment protocol, and our data lacked detailed information on in-hospital treatment (e.g., drug administrations, details of mechanical ventilation, and adverse events that occurred during treatment). Third, the number of PCR tests in Japan was less than that in other countries in the early phase of the outbreak. Nevertheless, as the present study was a case series of patients who received invasive mechanical ventilation, the probability of misclassification should be low in this population.

In conclusion, among the 125 patients with laboratory-confirmed COVID-19 who received invasive mechanical ventilation, 97% were intubated within 14 days from clinical onset, and the 30-day mortality rate was 24.0%. The present prefecture-level real-world evidence from Japan should facilitate preparedness against COVID-19.

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Conflict of interest

All authors declare no conflict of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.10.051.

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