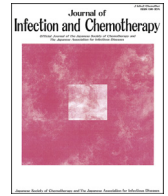




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Note

Experience of 101 patients with coronavirus infectious disease 2019 (COVID-19) at a tertiary care center in Japan



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ABSTRACT

Introduction: Clusters of novel coronavirus infectious disease of 2019 (COVID-19) have spread to become a global pandemic imposing a significant burden on healthcare systems. The lack of an effective treatment and the emergence of varied and complicated clinical courses in certain populations have rendered treatment of patients hospitalized for COVID-19 difficult.

Methods: Tokyo Metropolitan Tama Medical Center, a public tertiary acute care center located in Tokyo, the epicenter of COVID-19 in Japan, has been admitting patients with COVID-19 since February 2020. The present, retrospective, case-series study aimed to investigate the clinical course and outcomes of patients with COVID-19 hospitalized at the study institution.

Results: In total, 101 patients with COVID-19 were admitted to our hospital to receive inpatient care. Eleven patients (10.9%) received ECMO, and nine patients (8.9%) died during hospitalization after COVID-19 was diagnosed. A history of smoking and obesity were most commonly encountered among patients with a complicated clinical course. Most patients who died requested to be transferred to advanced palliative care in the early course of their hospitalization.

Conclusions: Our experience of caring for these patients demonstrated a relatively lower mortality rate and higher survival rate in those with extracorporeal membrane oxygenation placement than previous reports from other countries and underscored the importance of proactive, advanced care planning in the early course of hospitalization.

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1. Introduction

The first cluster of novel pneumonia cases, later designated coronavirus disease of 2019 (COVID-19), was reported in Wuhan, China in late December 2019. An infected individual returning from China on January 16, 2020 was identified as the first carrier of COVID-19 in Japan. In early February 2020, another cluster of cases was confirmed among passengers on a cruise ship. Since then, COVID-19 has spread rapidly throughout Japan, with Tokyo being one of the epicenters of the infection in the nation.

The rapid spread of COVID-19 has overwhelmed the capacity of many hospitals to provide care, causing a shortage of medical

resources, including personal protective equipment (PPE), various medical supplies, and hospital beds. Moreover, healthcare personnel continue to face a significantly increased risk of contracting COVID-19 while providing patient care.

Although the clinical features and treatment course of patients with COVID-19 have been reported from various parts of the world, reports from Japanese institutions have been scarce [1,2]. The present study aimed to investigate the clinical course and outcomes of patients with COVID-19 who were hospitalized at a Japanese tertiary care center.

2. Patients and methods

The present study was conducted at Tokyo Metropolitan Tama Medical Center, a 790-bed, public tertiary care center with 29

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subspecialties, located in Tokyo, Japan. The study institution has been admitting patients with COVID-19 since February 2020, and critically ill patients have been referred to our institution by other acute care hospitals located in Tokyo. Patients with the diagnosis of COVID-19 confirmed by polymerase chain reaction (PCR) tests of nasopharyngeal swabs or sputum between February 15, 2020 and June 7, 2020 were included. The patients were placed in a negative pressure room in a designated unit or intensive care unit and treated by staff from the Department of Medicine and the Department of Critical Care.

The demographic characteristics of the patients, including clinical and microbiological data, were collected during hospitalization. Outcome data on COVID-19 cases, including all-cause mortality rate during hospitalization, the patients' hospital discharge status, length of hospital stay (LOHS), and complications during hospitalization, were also collected. The decision of hospital discharge for patients with COVID-19 was at the discretion of inpatient providers, based on clinical improvement assessed by inpatient providers and two consecutive negative PCR results.

A complicated clinical course was defined as any patient dying during hospitalization or a patient receiving an invasive intervention, including intubation with ventilatory support, extracorporeal membrane oxygenation (ECMO), and renal replacement therapy. In-hospital clinical guidelines for COVID-19 care list the indications for ECMO placement (age ≤ 65 , progressive deterioration with PEEP ≥ 10 mmH₂O and P/F < 100 , no irreversible underlying diseases or terminal stage of cancer), and critical care physicians made the final decision on its use. The institutional review board at Tokyo Metropolitan Tama Medical Center approved this project. Obtaining consent from the patients was waived because the waiver or alteration would not adversely affect the rights and welfare of the patients.

3. Results

During the study period, 4786 patients were hospitalized. PCR testing for COVID-19 was performed for 1051 patients, and 130 PCR tests were newly positive (including positive results from other hospitals). Of the 130 patients with a novel diagnosis of COVID-19, 101 were hospitalized, and the remaining 29 patients were either admitted to another hospital or a designated housing facility or were quarantined at home under close observation by local department of health (DOH) personnel.

Of the 101 patients who were admitted to our hospital, one patient was transferred from the contaminated cruise ship, and another patient was an evacuee from Wuhan, China. The demographic characteristics and clinical outcomes of hospitalized patients with COVID-19 are shown in [Table 1](#). The initial presentations and laboratory findings of these patients are shown in [Supplementary Table 1](#). The median age of the hospitalized patients was 60 years (range: 17–97 years), 60.4% (61/101) were male, and 98 (97.0%) were of Japanese ethnicity. In terms of clinical outcomes, 9 patients (8.9%) died during hospitalization after the diagnosis of COVID-19 whereas 92 patients survived. The median LOHS for the patients was twelve days (range: 2–45 days) overall, eleven days (range 5–45 days) in those without a complicated clinical course, and 21 days (range 2–44 days) in those with a complicated clinical course. Of the patients with a complicated clinical course, 16 (15.8%) were intubated, 11 (10.9%) received ECMO, and five (5.0%) underwent renal replacement therapy. Among the preexisting baseline characteristics, a history of smoking, alcohol consumption, and obesity (BMI ≥ 25) were factors more commonly encountered among patients with a complicated clinical course ([Table 2](#)).

The details of the patients who died during hospitalization are shown in [Table 3](#). Except for two patients who were on ECMO,

seven patients in the early course of hospitalization asked the clinical team to make no attempt at resuscitation (i.e., DNAR) probably because of their older age or multiple comorbidities. Comfort measures order set was implemented during the early course of hospitalization for six of the nine (66.7%) patients who died.

4. Discussion

The current study is a case series of hospitalized patients with COVID-19 at a Japanese tertiary care center. Given the scarcity of case series studies of hospitalized patients with COVID-19 in Japan, most of which enrolled smaller sample sizes or focused on evacuees from Wuhan or the cruise ship, our study, conducted at a hospital located in the epicenter of COVID-19 in Japan, provided more comprehensive data and clinical and care-related insights into patients with COVID-19. A few patients received potentially effective drugs against COVID-19, including favipiravir, sarilumab, and lopinavir/ritonavir whereas common medical interventions consisted of supplemental oxygen and preemptive antimicrobial therapy targeting concomitant bacterial pneumonia. Our clinical data on patients with COVID-19 highlighted the lower overall mortality rate and higher probability of survival in those receiving ECMO than in patients in other parts of the developed world [3–6].

While previous studies reported various figures for the median age of patients hospitalized with COVID-19, ranging from 42 to 73 years [7–13], the age distribution in the current study was broadly similar to that reported by studies in the United States, the United Kingdom, and Italy [11–13]. However, the mortality rate reported in the latter studies ranged from 26 to 33% in contrast to the rate of 8.9% in the current study. Although the difference in the threshold of hospitalization might influence the mortality rate, the generally lower mortality rate among populations in Asia in contrast to populations in the US or Europe may at least account for part of the discrepancy. For example, case series from China and Singapore in the early stages of the pandemic reported a lower mortality rate (ranging from 0% to 4.3%) among patients with COVID-19 [7,8,10]. Moreover, a population-based comparison of mortality rates further corroborated this finding [3]. Although it remains unclear why the mortality rate should be lower among patients of Asian ethnicity, various factors have been proposed, such as the difference in the incidence of critical complications (e.g., thromboembolic events) due to COVID-19, patient demographics (e.g., a large, elderly population, the presence of comorbidities), and unknown individual factors. Moreover, hospital-level differences (e.g., the amount of testing, characteristics of the healthcare systems, and crippling of hospitals due to a high volume of patients), and national-level differences (e.g., national preparedness strategies) have also been adduced as possible contributory factors.

In total, nine patients with COVID-19 in our hospital died. Except for two patients receiving ECMO placement, the remaining seven patients expired pursuant to their request not to attempt resuscitation (DNAR) in the natural progression of their clinical course rather than due to clinical deterioration despite escalating medical therapy. All seven patients had dyspnea when they first visited our hospital, and the patients and medical staff discussed their code status soon after admission. Six patients requested to be transferred to advanced palliative care during the early course of their hospitalization. This fact illustrates the importance of advanced care planning in the early course of illnesses for improving patients' comfort level, preserving patients' dignity, and prioritizing the use of medical resources for those most in need.

At our hospital, 11 patients with respiratory failure (10.9%; 11/101) required ECMO placement, and nine patients (81.8%; 9/11) recovered and were discharged. Most patients with ECMO who

Table 1
Demographic characteristics and clinical outcomes of the COVID-19 patients.

| Characteristics | Overall (N = 101) |
|--|-------------------|
| Demographic characteristics | |
| Age, year, median, (range) | 60 (17–97) |
| Male | 61 (60.4) |
| Japanese ethnicity | 98 (97.0) |
| Occupational status | |
| Healthcare personnel | 6 (5.9) |
| Government employee | 8 (7.9) |
| Business personnel | 41 (40.6) |
| Unemployed | 46 (45.5) |
| Exposure to COVID-19 | |
| Close contact with COVID-19 patients while providing patient care (healthcare personnel) | 2 (2.0) |
| Close contact with COVID-19-positive individuals outside healthcare settings | 46 (45.5) |
| Cruise ship passengers | 1 (1.0) |
| Evacuees from Wuhan, China | 1 (1.0) |
| Unknown | 51 (50.5) |
| Location prior to hospitalization | |
| Home | 63 (62.4) |
| Residential care facility for the elderly | 5 (5.0) |
| Acute care hospital | 20 (19.8) |
| Long-term care facility | 13 (12.9) |
| Clinical characteristics | |
| Length of stay, median (range) | 12 (2–45) |
| Treatment details | |
| Supplemental oxygen | 57 (56.4) |
| Mechanical ventilation | 16 (15.8) |
| ECMO placement | 11 (10.9) |
| Renal replacement therapy | 5 (5.0) |
| Inpatient medication for COVID-19 | |
| Systemic glucocorticoid | 2 (2.0) |
| Lopinavir/ritonavir | 4 (4.0) |
| Sarilumab | 3 (3.0) |
| Favipiravir | 2 (2.0) |
| Ciclesonide inhaler | 2 (2.0) |
| Antimicrobial agent | 45 (44.6) |
| Antifungal agent | 5 (5.0) |
| Complications during hospitalization | |
| Cardiovascular event | 0 (0.0) |
| Acute respiratory distress syndrome | 23 (22.8) |
| Bacterial pneumonia | 11 (10.9) |
| Delirium | 11 (10.9) |
| Aseptic meningitis | 1 (1.0) |
| Cerebrovascular accident | 1 (1.0) |
| Pulmonary embolism/deep vein thrombosis | 4 (4.0) |
| Acute kidney injury | 16 (15.8) |
| Discharge status | |
| Died during hospitalization ^a | 9 (8.9) |
| Home | 27 (26.7) |
| Residential care facility for the elderly | 1 (1.0) |
| Transfer to acute care hospital ^b | 33 (32.7) |
| Transfer to long-term care facility | 17 (16.8) |
| Transfer to housing facility designated for COVID-19 patients | 14 (13.9) |

NOTE Data are presented as a number (%) unless otherwise specified. COVID-19, coronavirus disease of 2019; ECMO, extracorporeal membrane oxygenation.

^a Eight patients died within 30 days at our institution and one patient died on hospital day 38.

^b Hospitalized patients with COVID-19 were transferred to smaller hospitals to continue medical care.

survived (8/9) were directly admitted to our hospital. The data on the outcomes of ECMO use in COVID-19 patients are still scarce. A US study on COVID-19 reported that about one-third of 32 patients with ECMO placement died [4], and a multicenter, retrospective study of 333 patients with ECMO at 90 institutions in Europe demonstrated a mortality rate as high as 17.1%, with the rates varying significantly between institutions [5]. Since our institution is one of several referral centers handling ECMO placement in Tokyo, Japan, our preliminary data suggesting a higher survival rate associated with ECMO use warrants further study.

Although the present study was unable to identify the factors independently associated with a complicated clinical course in patients with COVID-19 due to the small sample size, certain underlying conditions and clinical courses might be more frequently

observed in COVID-19 patients with a complicated clinical course. In line with the findings of previous studies, history of smoking and overweight were considered to be risk factors of severe COVID-19 [7,14].

The present study has several limitations. First, as a single-center study, its findings may not be representative of clinical outcomes at other Japanese institutions. Because it was retrospective, some important information may not have been fully documented. Potentially effective medical interventions were unable to be examined due to the small number of patients in this study receiving the medications of interest. Lastly, the factors independently associated with COVID-19 were not able to be ascertained due to the small sample size.

Table 2
Comparison of baseline characteristics between COVID-19 patients with or without a complicated clinical course.

| Characteristics | Without a complicated clinical course (n = 78) | With a complicated clinical course (n = 23) |
|---------------------------------------|--|---|
| Age ≥ 65 | 28 (35.9) | 10 (43.5) |
| Body mass index (n = 94) ^a | | |
| <25 | 44/73 (60.3) | 7/21 (33.3) |
| ≥25 | 29/73 (39.7) | 14/21 (66.7) |
| History of smoking | 17 (21.8) | 12 (52.2) |
| Alcohol use | 25 (32.1) | 13 (56.5) |
| Comorbidities/past medical history | | |
| Congestive heart failure | 1 (1.3) | 0 (0.0) |
| History of myocardial infarction | 5 (6.4) | 1 (4.3) |
| History of asthma | 9 (11.5) | 0 (0.0) |
| Chronic lung disease | 2 (2.6) | 3 (13.0) |
| Active solid organ malignancies | 3 (3.9) | 0 (0.0) |
| Diabetes mellitus | 17 (21.8) | 3 (13.0) |
| Hypertension | 29 (37.2) | 8 (34.8) |
| Peptic ulcer disease | 4 (5.1) | 1 (4.3) |
| Cerebrovascular disease | 6 (7.7) | 2 (8.6) |
| Chronic liver disease | 3 (3.8) | 0 (0.0) |
| Chronic kidney disease | 2 (2.6) | 0 (0.0) |
| Connective tissue disease | 0 (0.0) | 1 (4.3) |
| Dementia | 6 (7.7) | 2 (8.7) |
| Psychiatric illness | 14 (17.9) | 0 (0.0) |
| HIV infection | 0 (0.0) | 0 (0.0) |
| Home medications | | |
| ACEs or ARBs | 18 (23.1) | 3 (13.0) |
| Statins | 13 (16.7) | 4 (17.4) |

NOTE. Data are presented as a number (%) unless otherwise specified.

Abbreviations: HIV, human immunodeficiency virus; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

^a Data for body mass index were missing for seven patients.

Table 3
Characteristics of the 9 deceased patients with COVID-19.

| Age | Sex | Comorbidity | LOS, days | ECMO | DNAR orders | Comfort measure order set prior to death |
|-----|-----|-----------------------|-----------|------|-------------|--|
| 49 | F | Untreated DM, obesity | 38 | Yes | Day 36 | Day 37 |
| 64 | M | AAV, IP | 8 | No | Day 1 | Day 3 |
| 72 | M | HTN, CVA, COPD | 12 | No | Day 2 | Day 6 |
| 75 | M | IP, COPD, leukemia | 2 | No | Day 1 | Day 1 |
| 76 | M | HTN, stroke | 8 | No | Day 1 | Day 3 |
| 78 | M | None | 6 | No | Day 1 | No |
| 81 | M | HTN, TB | 21 | Yes | Day 19 | Day 19 |
| 87 | F | AD | 10 | No | Day 1 | Day 5 |
| 96 | F | HTN, CHF | 4 | No | Day 1 | Day 1 |

NOTE. LOS, length of stay; ECMO, extracorporeal membrane oxygenation; DNAR, do not attempt resuscitation; DM, diabetes mellitus; AAV, ANCA-associated vasculitis; IP, interstitial pneumonitis; HTN, hypertension; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; TB, tuberculosis; AD, Alzheimer dementia; CHF, congestive heart failure.

The present study revealed the current practices and outcomes in the treatment of patients hospitalized with COVID-19 at a Japanese tertiary care hospital. Some favorable clinical outcomes, including a relatively low mortality rate and high success rate for ECMO treatment, were observed although these rates might have been influenced by various, unexamined factors. Proactive advanced care planning in the early course of illness was also shown to be essential in improving the quality of patient care and the utilization of medical resources.

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Author contribution

Study design: H·H., Y.T., K·S.
Data collection: S·H., K·Y., Y.T., A.T, Y·U.
Draft manuscript preparation: K·Y.
Revise manuscript: All the authors.

Provide patient care: Physicians on the Tokyo Metropolitan Tama Medical Center COVID 19 treatment team.

Declaration of competing interest

All the authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiac.2020.11.024>.

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