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Original article

Clinical course of patients with chronic limb-threatening ischemia developing COVID-19☆

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ABSTRACT

Background: The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2, has overwhelmed healthcare systems. Patients with lower extremity artery disease are at high risk of cardiovascular events, of whom chronic limb-threatening ischemia (CLTI) is the most severe manifestation of peripheral artery disease with an increased risk of mortality compared to patients with intermittent claudication. However, the clinical course of CLTI patients with COVID-19 has not been reported.

Methods: We retrospectively surveyed clinical course for 25 CLTI patients who developed COVID-19 during the "sixth wave" of the pandemic in Japan, which started in January 2022. The primary outcome measure was the 30-day mortality after the diagnosis of COVID-19. We also compared the mortality risk of the 18 COVID-19 patients who underwent initial endovascular treatment with that of 1867 CLTI patients who received initial endovascular treatment before December 2019 (i.e. before the COVID-19 pandemic) (control group). Cox proportional hazard regression model was used to evaluate the effect of COVID-19 on the mortality. To confirm the robustness of these results, we added the analysis with inverse probability weighting (IPW) based on the propensity score for the COVID-19.

Results: The 30-day mortality after the diagnosis of COVID-19 reached 20 %; the 95 % confidence interval (CI) of the proportion was calculated to be 7 % to 41 % by the Clopper-Pearson exact method. Cox regression analysis demonstrated the mortality risk was significantly higher in patients developing COVID-19 than in control group [adjusted hazard ratio, 3.08 (95 % CI, 1.13–8.37); $p = 0.027$]. The IPW analysis also confirmed the significant association of COVID-19 with the mortality risk [hazard ratio, 3.97 (95 % CI 1.54–10.21, $p = 0.004$)].

Conclusion: In CLTI patients, the 30-day mortality after the diagnosis of COVID-19 reached 20 % (95 % CI, 7 % to 41 %) under the pandemic in January 2022, and patients developing COVID-19 had a significantly higher mortality risk than those treated before the pandemic.

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a worldwide public health issue [1]. In Japan, we are now facing 'the sixth wave' in January 2022, which is mainly caused by the B.1.1.529 (omicron) variant [2]. Patients with lower extremity artery disease are at high risk of cardiovascular events, of whom chronic limb-threatening ischemia (CLTI) is the most severe manifestation of peripheral artery disease with an increased risk of mortality compared to patients with intermittent claudication [3,4]. However, the clinical course of patients with CLTI with COVID-19 has not been fully investigated.

Materials and methods

Patients

This was a single-center, retrospective, observational study. A total of 25 CLTI patients acquired SARS-CoV-2 infections in our hospital in January 2022. Of these, 18 patients were hospitalized due to the initial

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endovascular treatment. We followed short-term clinical course for the 25 CLTI patients who developed COVID-19. We also compared the mortality risk of the 18 COVID-19 patients who underwent initial endovascular treatment with that of 1867 CLTI patients who received initial endovascular treatment before December 2019 (i.e. before the COVID-19 pandemic) (control group). The study was approved by the Medical Ethics Committees of Kansai Rosai Hospital and it adhered to the tenets of the Declaration of Helsinki. The requirement for the patients' written informed consent was waived because this was observational research without intervention or invasiveness and did not use human biological specimens, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study has been made available to the public.

Outcome measures

The primary outcome measure was the 30-day mortality after the diagnosis of COVID-19. At the time of diagnosis, severity of COVID-19, symptoms, respiratory status including the requirement of mechanical ventilation and extracorporeal membrane oxygenation (ECMO) were also evaluated. Severity of COVID-19 was defined according to the official guide in Japan [5], as follows: Mild, SpO2 ≥ 96 %, no respiratory symptoms or coughing only and no shortness of breath; Moderate I, 93 % < SpO2 < 96 %, shortness of breath and pneumonia findings; Moderate II, SpO2 ≤ 93 %, oxygen administration required; Severe, admission to intensive care unit or mechanical ventilator required.

Statistical analysis

All results are expressed as mean ± SD and median (interquartile range) for continuous variables with and without normal distribution. Continuous variables were compared between the groups using the unpaired *t*-test or Mann-Whitney *U* test, based on the data distribution. Categorical variables were compared between the two groups with the chi-square test or Fisher's exact test, as appropriate. An unavailable Cox proportional hazard regression model was used to evaluate the risk factors for mortality in patients with COVID-19. Results of the model are presented as the hazard ratio (HR) and 95 % confidence interval (CI). In addition, a multivariable Cox proportional hazard regression model was used to evaluate the effect of COVID-19 on the mortality while adjusting for covariates including age, sex, body mass index, Rutherford class, hypertension, diabetes mellitus, dyslipidemia, current smoking, chronic renal failure (estimated glomerular filtration rate < 30 mL/min/1.73m^2), hemodialysis, coronary artery disease, stroke, and reduced left ventricular ejection fraction (<50 %). Results of the model are presented as the HR and 95 % CI. To confirm the robustness of these results, we added the analysis with inverse probability weighting (IPW) based on the propensity score for the COVID-19. A logistic regression model was applied to predict the probability of COVID-19 with the following baseline covariates: age, sex, body mass index, Rutherford class, hypertension, diabetes mellitus, dyslipidemia, current smoking, chronic renal failure, hemodialysis, coronary artery disease, stroke, and reduced left ventricular ejection fraction. Then we calculated the HR of COVID-19 for mortality with IPW based on the propensity score.

All tests were two-sided with a 5 % significance level. The statistical analyses were performed with the IBM SPSS Statistics package ver. 26 (IBM Corp., Armonk, NY, USA) and R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Results

Patient characteristics

Of the 25 patients, 16 patients (64 %) were diagnosed with COVID-19 by polymerase chain reaction test of nasopharyngeal swab and 10 patients (40 %) were by quantitative antigen test of nasopharyngeal swab. Baseline patient characteristics are shown in Table 1. Mean body mass index was 21.4 ± 4.4 kg/m^2. Eighteen patients (72 %) underwent daily hemodialysis. Patients with Rutherford category 4, 5, and 6 accounted for 12 %, 56 %, and 32 % of the population, respectively. Mean hemoglobin level was 9.8 ± 1.4 g/dL. Median C reactive protein level was 2.5 (0.6–5.1) mg/dL.

Table 1
Patient characteristics and laboratory data at the time of diagnosis as COVID-19.

	n = 25
Age, years	73.8 ± 4.8
Male, n (%)	16 (64)
Body mass index, kg/m^2	21.4 ± 4.4
Previous history, n (%)	
Hypertension	14 (56)
Diabetes mellitus	19 (76)
Dyslipidemia	12 (48)
Current smoking	4 (16)
Chronic renal failure	21 (84)
Hemodialysis	18 (72)
Coronary artery disease	21 (84)
Stroke	7 (28)
Rutherford class, n (%)	
IV/V/VI	3 (12)/ 14 (56)/ 8 (32)
White blood cell, ×10^{3}μ/L	5.4 ± 2.1
Lymphocytes, /μL	643 (342–818)
Hemoglobin, g/dL	9.8 ± 1.4
Platelet count, ×10^3/μL	159.9 ± 65.0
Total bilirubin, mg/dL	0.3 (0.2–0.4)
Albumin, g/dL	2.7 ± 0.6
Alanine transaminase, U/L	9.0 (4.0–22.5)
Lactate dehydrogenase, U/L	178.5 (149.5–198.5)
Creatine kinase, U/L	33.0 (18.0–51.5)
Blood urea nitrogen, mg/dL	41.9 (25.5–51.6)
Estimated glomerular filtration rate, mL/min/1.73m^2	5.96 (4.9–12.0)
C-reactive protein, mg/dL	2.5 (0.6–5.1)
Prothrombin time, second	13.1 (12.1–15.0)
D-dimer, μg/mL	1.6 (0.7–3.0)

Data are mean ± standard deviation or median (interquartile range) or number (%).

Clinical course

Clinical courses after the diagnosis of COVID-19 are shown in Table 2. Severity of COVID-19 was judged as mild for 24 patients (96 %) and 1 patient, undergoing home oxygen therapy for chronic obstructive pulmonary disease before the infection, was categorized as moderate I. At the diagnosis of COVID-19, no patient was complicated with

Table 2
Clinical course after the diagnosis of COVID-19.

	n = 25
Diagnosis method, n (%)	
Polymerase chain reaction test (nasopharyngeal swab)	16 (64)
Quantitative antigen test (nasopharyngeal swab)	10 (40)
Treatment with sotrovimab, n (%)	18 (72)
Severity at the time of diagnosis, n (%)	
Mild/ModerateI/ModerateII/Severe	24 (96)/ 1 (4)/ 0 (0)/ 0 (0)
Symptom, n (%)	
Fever	19 (76)
Cough	9 (36)
None	1 (4)
Pneumonia, n (%)	3 (12)
Oxygen demand, n (%)	6 (24)
Intensive care unit stay, n (%)	0 (0)
Mechanical ventilation, n (%)	0 (0)
Extracorporeal membrane oxygenation, n (%)	0 (0)
Mortality, n (%)	5 (20)

Data are number (%).

Table 3
Patient characteristics in CLTI patients with and without COVID-19.

	COVID-19 group (n = 18)	Control group (n = 1867)	*p*-value
Age, years	74.8 ± 8.2	73.9 ± 10.2	0.65
Male, n (%)	10 (56)	1161 (62)	0.63
Body mass index	21.3 ± 4.3	21.5 ± 3.7	0.86
Previous history, n (%)			
Hypertension	9 (50)	1275 (68)	0.13
Diabetes mellitus	13 (72)	1208 (65)	0.62
Dyslipidemia	9 (50)	692 (37)	0.33
Current smoking	2 (11)	382 (21)	0.26
Chronic renal failure	14 (78)	1100 (59)	0.15
Hemodialysis	11 (61)	1057 (57)	0.81
Coronary artery disease	15 (83)	956 (51)	0.008
Stroke	4 (22)	330 (18)	0.54
Rutherford class, n (%)			
IV/V/VI	2 (11)/ 10 (56)/ 6 (33)	319 (17)/ 1145 (61)/ 403 (22)	0.23
Left ventricular ejection fraction, %	51.8 ± 18.7	60.7 ± 13.3	0.063

Data are mean ± standard deviation or number (%).
CLTI, chronic limb-threatening ischemia COVID-19.

pneumonia, while two patients needed oxygen due to chronic obstructive pulmonary disease and congestive heart failure, respectively. Sotrovimab was administrated to 18 patients (72 %). No one stayed in the intensive care unit. Neither mechanical ventilation nor ECMO was used for all patients. However, 5 patients (20 %) died within 30 days after the diagnosis of COVID-19; the 95 % CI of the proportion was calculated to be 7 % to 41 % by the Clopper-Pearson exact method. The causes of death were bacterial pneumonia (3 patients; at 14, 20, and 26 days after the diagnosis of COVID-19), septic shock (1 patient; 17 days after the diagnosis), and sudden death (1 patient; 5 days after the diagnosis). The significant risk factors for mortality were body mass index [1 kg/m^2 increase, HR 0.76 (95%CI 0.58–0.995), $p = 0.046$], white blood cell count [1.0×10^3 μ/L increase, HR 0.47 (95%CI 0.27–0.84), $p = 0.011$], platelet count [1.0×10^3/μL increase, HR 0.98 (95%CI 0.96–0.998), $p = 0.028$], albumin [1 g/dL increase, HR 0.065 (95%CI 0.008–0.52), $p = 0.010$], and alanine transaminase [1 U/L increase, HR 1.06 (95%CI 1.01–1.13), $p = 0.034$], while hemodialysis was not [HR 0.55 (95%CI 0.092–3.32), $p = 0.52$].

Comparison between CLTI patients with COVID-19 and control group (before COVID-19 pandemic)

The patient characteristics were similar between patients with the COVID-19 group and the control group except for the previous history of coronary artery disease (Table 3). The crude HR for mortality of COVID-19 was 3.82 (95 % CI 3.82–1.41-10.34, $p = 0.008$), while the adjusted HR was 3.08 (95 % CI 1.13–8.37; $p = 0.027$). The IPW analysis also confirmed the significant association of COVID-19 with the mortality risk ($p = 0.004$); the HR was 3.97 (1.54–10.21) (Table 4).

Discussion

Although most of the patients showed mild severity, the 30-day mortality reached 20 % (95 % CI, 7 % to 41 %). Patients developing COVID-19 had a significantly higher mortality risk than those treated before the pandemic, with an adjusted HR of 3.08 (95 % CI, 1.13 to 8.37).

A systematic review and meta-analysis demonstrated that lymphopenia, thrombocytopenia, elevated D-dimer, elevated C reactive protein, elevated procalcitonin, elevated creatine kinase, elevated aspartate transaminase, elevated alanine transaminase, elevated creatinine and lactate dehydrogenase were independently associated with higher risk of poor outcomes in COVID-19 hospitalized patients [6]. In addition to these risk factors, low body mass index and low albumin were associated with morality in the current study. These factors were previously reported as risk factors of mortality for patients with advance peripheral artery disease [7,8]. Low body mass index and low albumin reflect malnutrition status, and we should pay attention to these parameters for CLTI patients with COVID-19.

In a retrospective, consecutive cohort study of CLTI patients with COVID-19 infection admitted at a single hospital in Brazil between March 2020 and March 2021, the in-hospital mortality rate was 40 % and all patients died due to COVID-19 pneumonia infection [9]. Although COVID-19 considerably increased the risks of mortality, disease progression, and hospitalization [5], the strategy against COVID-19 has been progressing. Vaccination with an mRNA COVID-19 vaccine was effective to prevent COVID-19 hospitalization and disease progression to death or mechanical ventilation [10,11]. Sotrovimab, which is a pansarbecovirus monoclonal antibody, reduced the risk of disease progression among high-risk patients with mild-to-moderate COVID-19 [12]. Few of the current study patients experienced the worsening of respiratory status by COVID-19 itself, which might be owed to those progresses against COVID-19. Nonetheless, the current study revealed the fact that the 30-day mortality reached 20 % (95 % CI, 7 % to 41 %), and COVID-19 was associated with three to four times higher mortality risk in CLTI patients. Although a series of strategies against COVID-19 might make the severity of COVID-19 milder, the clinical outcomes after COVID-19 development would have plenty of room for improvement, especially in CLTI patients. The higher mortality risk in the population would come partially from their advanced atherosclerosis and frailty.

This study has several limitations. First, the type of viral variant was not evaluated in this population. However, judging from the spread of omicron variant, infection of the variant would be dominant in the study population. Second, this study showed only short-term outcomes. Longer-term follow-up is necessary to evaluate the subsequent clinical outcomes in patients with CLTI. Finally, we recommended the intensive care such as mechanical ventilation and ECMO to the patients or the patients' family. However, they did not hope to undergo intensive treatment, and neither mechanical ventilation nor ECMO was used for all patients. The use of ECMO may change the outcome of this population.

Conclusions

In CLTI patients, the 30-day mortality after the diagnosis of COVID-19 reached 20 % (95 % CI, 7 % to 41 %) under the pandemic in January 2022, and patients developing COVID-19 had a significantly higher mortality risk than those treated before the pandemic.

Data availability

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

Table 4
Adjusted risk of COVID-19 on mortality.

Outcome	Crude HR		HR adjusted for covariates		HR based on IPW	
	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Mortality	3.82 (1.41–10.34)	0.008	3.08 (1.13–8.37)	0.027	3.97 (1.54–10.21)	0.004

CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting.

Declaration of competing interest

None to declare.

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