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Fungal infection-related conditions and outcomes in severe COVID-19: a nationwide case-control study

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Abstract

Background Fungal infections are significant complications of severe coronavirus disease 2019 (COVID-19). Although various risk factors for poor outcomes in patients with COVID-19 have been identified, clinical and treatment factors associated with fungal infections in patients with severe COVID-19 remain unclear. This study aimed to elucidate clinical factors associated with fungal infections during severe COVID-19 treatment.

Methods This was a post hoc analysis of the J-RECOVER study, a multicenter retrospective observational study involving patients with COVID-19 who required admission at 66 hospitals between January and September 2020. Inclusion criteria were ages ≥ 18 years, COVID-19 diagnosis with reverse-transcription polymerase chain reaction, and treatment with mechanical ventilation (MV). Patients who received antifungal drugs before MV were excluded. Potential predictors were identified through univariate analysis of patient and treatment characteristics between patients with- and those without fungal infection, which was defined as antifungal agent use for ≥ 5 days. To account for facility-specific data clustering, generalized estimating equations (GEE) were employed as adjusted analyses to calculate the relative risks of potentially associated factors. Two sensitivity analyses were performed with modified definitions for the two groups: patients who received antifungal drugs for ≤ 4 days were excluded, and fungal infection was re-defined as antifungal drug use for ≥ 14 days.

Results Among 4,915 patients in the J-RECOVER study, 559 adults with COVID-19 who required MV were included. Fungal infections occurred in 57 (10.2%) patients. Univariate analyses identified age, age ≥ 65 years, D-dimer level, remdesivir use, steroid use, and duration of steroid therapy as potential predictors of fungal infections. Multivariate analysis using GEE on these six factors revealed that only the duration of steroid use was significantly associated with an increased risk of fungal infection (odds ratio [OR] for a day increase: 1.01; 95% confidence interval [CI]: 1.00–1.01; $p < 0.001$). The two sensitivity analyses similarly showed that the duration of steroid use was associated with fungal infection (odds ratio for a day increase: 1.01; 95% CI: 1.00–1.01; $p < 0.001$ for both).

Conclusions In patients with severe COVID-19 requiring MV, each additional day of steroid use was associated with prolonged use of antifungal medications for ≥ 5 days.

Keywords COVID-19, Fungal infection, Steroid therapy, Mechanical ventilation, Risk factors

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Background

The clinical outcomes of coronavirus disease 2019 (COVID-19) have improved with the development of pharmacological therapy and critical care management. Severe acute respiratory syndrome coronavirus 2 has also changed in pathogenicity over time, resulting in less severe clinical outcomes, such as a shorter length of hospital stay and reduced mortality [1, 2]. A recent study reported that the mortality rate per 1,000 patients decreased from 4.48 in the first wave to 0.67 in the fifth wave [3].

However, some populations still suffer from severe pulmonary and organ dysfunction due to COVID-19. Some observational studies have suggested the risks of exacerbation, including hematologic malignancies, diabetes mellitus, chronic kidney disease, and co-infection with bacterial and/or fungal pathogens [4–8]. Particularly, patients with fungal infections during treatment for COVID-19 have been reported to more frequently require intensive care and suffer from mortality. Thus, minimizing such additional risks is another target for the management of COVID-19 [9].

While some underlying conditions that predispose patients to fungal infections are similar to those associated with unfavorable outcomes after COVID-19, modifiable risk factors for fungal infections also exist. A multicenter cohort study on patients with COVID-19 managed with mechanical ventilation (MV) found that the concomitant use of anti-interleukin (IL)−6 and steroids increased the incidence of fungal infections [10]. Additionally, another cohort study involving patients with COVID-19 in an intensive care unit (ICU) suggested that long-term and/or high-dose steroids could be risk factors for fungal coinfection [11]. Accordingly, this study aimed to elucidate the clinical factors associated with the incidence of fungal infection during COVID-19 treatment, focusing on potentially avoidable treatments.

Methods

Study design and setting

This was a secondary analysis of the J-RECOVER study [12]. The J-RECOVER study was conducted to investigate the clinical characteristics of COVID-19 and included patients diagnosed with moderate-to-severe COVID-19 (requiring oxygen and/or ICU admission) at 66 institutions in Japan between January and September 2020, during which two waves of increased number of patients with COVID-19 occurred. The J-RECOVER study included patients diagnosed with COVID-19 using a positive reverse transcription polymerase chain reaction (RT-PCR). The J-RECOVER study was conducted after obtaining approval from the institutional review board (IRB) to conduct research on human participants at participating institutions. The IRB of the Keio University School of Medicine approved this study on human participants (application number: 20200317). As the data in the study were anonymous, the requirement for informed consent was waived.

Study population

The inclusion criteria for this study were ages ≥ 18 years, COVID-19 diagnosis with RT-PCR, and MV usage. Patients who met the criteria were included in the study. Patients who received antifungal drugs before the initiation of MV were excluded.

Data collection and definitions

In the J-RECOVER study, data were collected from medical records and diagnosis procedure combinations at each participating facility, which is a method of calculating medical costs based on the diseases and details of medical treatment as defined by the Japanese Ministry of Health, Labour and Welfare; the format is standardized in Japan and recorded by physicians [13]. These data included the diagnosis at admission, comorbidities, Hugh-Jones classification [14], New York Heart Association (NYHA) classification documented at admission [15], dates and amounts of drugs, and discharge summaries. In this study, we investigated the Charlson comorbidity index [16], related comorbidities, smoking, Hugh-Jones classification, NYHA classification, consciousness, respiratory status, and blood test results as the background of the patient's condition.

Data on antifungal drugs, steroids, remdesivir, and tocilizumab were also retrieved. However, the types of antifungal drugs were not available in the database. The list of administered steroids, except for topical drugs, was presented in the supplementary Table 1, which included oral and intravenous medications. The duration of steroid use was also assessed. Moreover, the number of days from hospital arrival to MV and from the initiation of MV to the administration of antifungal drugs were calculated. Data on in-hospital mortality, length of hospital stay, and ventilator- and ICU-free days up to 28 days after admission were also obtained.

Outcome measures

The primary outcome was the fungal infection, which was defined as the administration of antifungal drugs for ≥ 5 consecutive days: antifungal drugs should have been discontinued within 5 days if culture results returned negative for fungus, which generally takes less than 5 days. Culture results for fungal infections were not available in the database.

Data preparation and sample size estimation

The sample size for implementing multivariate logistic regression analysis with five possible risk factors was estimated to be at least 50 patients with fungal infections. Given that a quarter of the patients with COVID-19 who were treated with MV would have fungal infections based on previous studies, at least 200 patients with COVID-19 needed to be included in this study.

Statistical analysis

Patient characteristics are presented as number (%) or median (interquartile range) and were compared between patients with- and those without fungal infection. Univariate analysis was performed for each factor of patient characteristics and clinical consequences using Chi-squared tests or Mann–Whitney U tests, as appropriate, and the standardized mean difference was calculated to show substantial differences in each variable. Then, clinical factors with a substantial difference (standardized mean difference ≥ 0.3) were considered potentially relevant factors. Generalized estimating equation (GEE) models were used to investigate the factors associated with fungal infection, in which the potentially relevant factors obtained in the univariable analyses were entered.

We performed two sensitivity analyses. First, patients with ≤ 4 days of antifungal drug use, who were originally included as those without fungal infection, were excluded, and GEE analyses were repeated with the same variables as the original model. Second, fungal infection was re-defined as administration of antifungal drugs for ≥ 14 consecutive days, and GEE analyses were performed.

Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 29.0; IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA).

Results

Characteristics of patients

Among the 4,700 patients in the J-RECOVER study, 559 adult patients diagnosed with COVID-19 were treated with MV and met all inclusion criteria. The patients included in the analysis were categorized into 57 and 502 patients with- and without fungal infections, respectively (Fig. 1).

Patient characteristics are shown in Table 1. The median age was higher in patients with fungal infection compared to those without (72.0 [63.5–77.5] vs. 66.0 [55.0–75.0]). The frequency of steroid use was higher in patients with fungal infections (48 [84.2%] vs. 281 [56.0%]), whereas dexamethasone was administered similarly to patients with- and those without fungal infections. The duration of steroid therapy was longer in patients with fungal infection (16.0 [4.5–32.0] vs. 2.0 [0.0–10.0] days).

Regarding the duration of antifungal treatment, most patients were treated for 1–3 weeks, with a 2-week administration being the most frequent (Fig. 2).

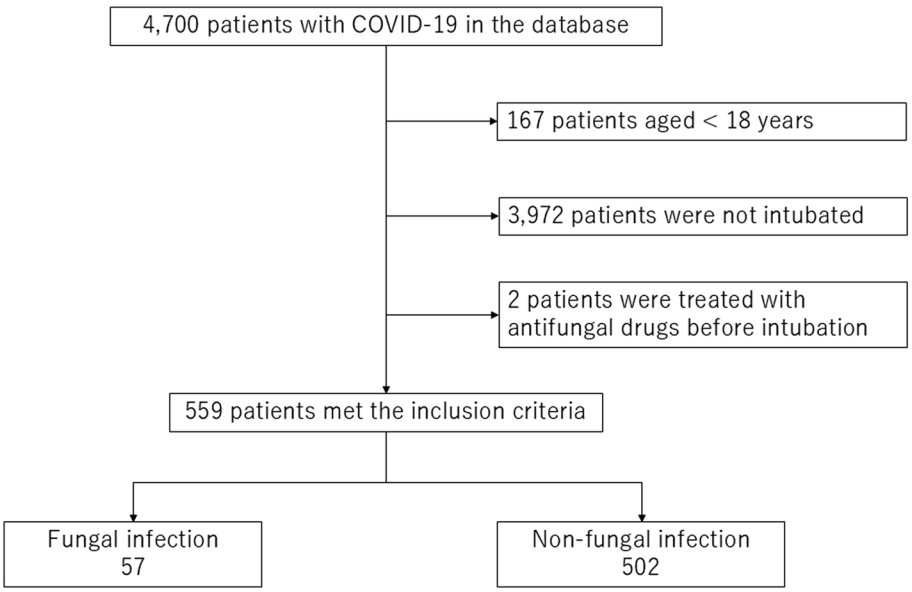

Fig. 1 Patient flow diagram. A total of 4,915 patients with coronavirus disease 2019 (COVID-19) were included in the J-RECOVER database. A total of 559 patients met the inclusion criteria. Of these patients, 57 fulfilled the definition of fungal infection and 502 were classified as having non-fungal infections

Table 1 Characteristics of patients with and without fungal infection

	With fungal infection		Without fungal infection		Standardzed Difference	*p* value
Case	57		502			
Age, years, median (IQR)	72.0	(63.5-77.5)	66	(55.0-75.0)	0.374	0.010
Age, ≥65, n(%)	41	(71.9%)	270	(53.8%)	0.382	0.011
Sex,male, n (%)	43	(75.4%)	398	(79.3%)	0.092	0.496
Charlson index, median (IQR)	0	(0-1)	0	(0-1)	0.040	0.689
Comorbidity, n (%)						
Chronic lung disease	0	(0.0%)	1	(0.2%)	0.063	1.000
Diabetes	14	(24.6%)	139	(27.7%)	0.071	0.754
HIV/AIDS	0	(0.0%)	1	(0.2%)	0.063	1.000
Malignancy	0	(0.0%)	12	(2.3%)	0.221	0.622
Chronic kidney disease	5	(8.8%)	15	(3.0%)	0.248	0.043
Social history						
Smoking, n (%)	11	(33.3%)	119	(41.0%)	0.160	0.457
Chronic cardiopulmonary status						
Hugh-Jones classification, > III, n (%)	9	(15.8%)	79	(15.7%)	0.001	1.000
NYHA functional classification, > II, n (%)	1	(1.8%)	5	(1.0%)	0.065	0.477
Status on hospital arrival						
GCS, median (IQR)	14.5	(5.5-15.0)	15	(8.0-15.0)	0.163	0.094
Respiratory rate, /min, median (IQR)	21	(15.0-26.0)	22	(18.0-26.0)	0.149	0.202
Oxygen requirement, ≥ 4 L/ min, n (%)	23	(40.4%)	206	(41.0%)	0.014	1.000
SOFA, hemodynamic score, median (IQR)	0	(0-0)	0	(0-0)	0.144	0.338
Blood test at time of admission, median (IQR)						
WBC, 10^3 /μL	7.2	(5.1-9.6)	7	(5.4-10.4)	0.009	0.848
CRP, mg/dL	13.3	(6.1-25.8)	10.8	(5.7-16.7)	0.186	0.041
D-dimer, μg/dL	2.6	(1.3-9.3)	1.7	(0.9-4.3)	0.314	0.036
Lactate, ≥ 2 mmol/L, n (%)	7	(12.3%)	55	(15.2%)	0.041	0.823
Status at the time of intubation						
PF ratio, mmHg, median (IQR)	142	(106.0-198.9)	162	(121.3-224.5)	0.239	0.087
SOFA, hemodynamic score, median (IQR)	0	(0-0)	0	(0-0)	0.044	0.598
Lactate, ≥ 2 mmol/L, n (%)	6	(12.5%)	46	(10.3%)	0.046	0.620
Medications, n (%)						
Remdesivir, n (%)	7	(12.3%)	130	(25.9%)	0.352	0.023
Tocilizumab, n (%)	10	(17.5%)	45	(9.0%)	0.255	0.056
Dexamethasone, n (%)	9	(15.8%)	107	(21.3%)	0.143	0.391
Steroid, n (%)	48	(84.2%)	281	(56.0%)	0.648	<0.001
Days during any steroid therapy, median (IQR)	16.0	(4.5-32.0)	2.0	(0-10.0)	0.805	<0.001
Days from arrival to intubation, median (IQR)	0	(0-2)	0	(0-1)	0.024	0.896
Days from symptom onset to intubation, median (IQR)	8	(5-10)	8	(6-11)	0.208	0.087
Days from mechanical ventilation to antifungal drugs, median (IQR)	15.0	(8.0-21.5)	15	(8.0-19.5)	0.069	0.804

COVID-19 Coronavirus disease 2019, *IQR* Interquartile range, *HIV* Human immunodeficiency virus, *AIDS* Aquired immune deficiency syndrome, *NYHA* New York Heart Association, *GCS* Glasgow Coma Scale, *SOFA* Sequential Organ Failure Assessment, *WBC* White blood cell count, *CRP* C-reactive protein, *PF ratio* ratio of partial pressure of oxygen and fraction of inspired oxygen

Higher in-hospital mortality, longer hospital stays, and shorter ventilator- and ICU-free days up to day 28 were observed in patients with fungal infections than in those without fungal infections (Table 2).

Predictive factors for fungal infection

Age, Age ≥ 65 years old, D-dimer, remdesivir, steroid, and days of steroid therapy were significantly associated with prolonged use of antifungal drug for ≥ 5 days

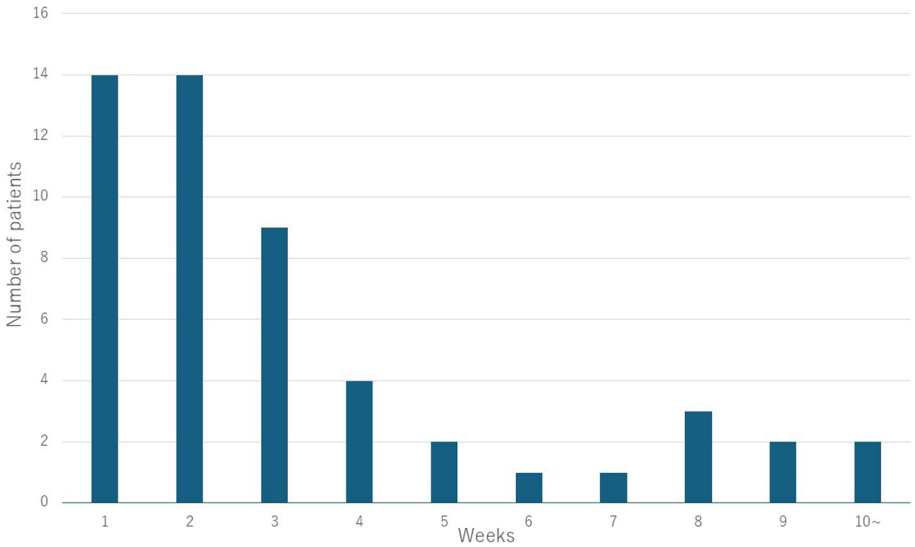

Fig. 2 Duration of antifungal drug administration in patients with fungal infection. Histograms show the number of cases that met the definition of fungal infection for each period of antifungal drug administration. Most treatments were administered for 1–3 weeks, with 2 weeks being the most common

Table 2 Outcomes of patients with and without fungal infection

	With fungal infection		Without fungal infection		*p* value
Mortality, n(%)	32	(56.1%)	112	(22.3%)	<0.001
Length of hospital stay, median(IQR)	36	(26.5-72.5)	20	(11.0-31.0)	<0.001
Ventilator-free days to day 28 after intubation, median(IQR)	11.5	(0-20.3)	25	(18.0-27.0)	<0.001
ICU-free days to day 28 after admission, median (IQR)	0	(0-0)	12	(0-19.0)	<0.001

IQR Interquartile range, *ICU* Intensive care unit

Table 3 Odds ratio of potential predictors for fungal infection

Variable	Odds ratio	95% confidence interval	*p* value
Age	1.00	1.00-1.00	0.975
Age, ≥65	1.05	0.96-1.14	0.275
D-dimer	1.00	1.00-1.00	0.079
Remdesivir	0.95	0.89-1.02	0.129
Steroid	0.98	0.92-1.05	0.575
Days during any steroid therapy	1.01	1.00-1.01[a]	<0.001

[a] Actual interval was 1.004 to 1.01

Table 4 Sensitivity analysis in patients without less than five days of antifungal medication

Variable	Odds ratio	95% confidence interval	*p* value
Age	1.00	1.00-1.00	0.911
Age, ≥65	1.05	0.96-1.14	0.300
D-dimer	1.00	1.00-1.00	0.084
Remdesivir	0.95	0.89-1.02	0.138
Steroid	0.99	0.92-1.05	0.691
Days during any steroid therapy	1.01	1.00-1.01[a]	<0.001

[a] Actual interval was 1.004 to 1.01

based on univariate analyses (Table 1); therefore, they were entered into the GEE model. The GEE model showed the duration of steroid treatments as the only predictor for fungal infection in patients with severe COVID-19 (odds ratio [OR] in 1-day increase of steroid use, 1.01; 95% confidence interval [CI], 1.004–1.01; $p < 0.001$; Table 3).

Sensitivity analyses after excluding patients with 1–4 days of antifungal medication use and redefining fungal infection as antifungal treatment ≥ 14 days also revealed that the days of steroid use was a predictor of fungal infection (OR in a 1-day increase of steroid use, 1.01; 95% CI, 1.004–1.01; $p < 0.001$ in both sensitivity analyses;

Table 5 Sensitivity analysis with re-defining fungal infection

Variable	Odds ratio	95% confidence interval	*p* value
Age	1.00	1.00-1.00	0.938
Age, ≥65	1.03	0.96-1.11	0.407
D-dimer	1.00[a]	1.00-1.00	0.042
Remdesivir	0.99	0.94-1.03	0.560
Steroid	0.98	0.93-1.03	0.413
Days during any steroid therapy	1.01	1.00-1.01[b]	<0.001

Fungal infection was re-defined as antifungal treatment ≥14 days

[a] Actual odds ratio was 1.0020 (95% Confidence Interval was 1.0001 to 1.0040)

[b] Actual interval was 1.004 to 1.01

Tables 4 and 5). Moreover, another sensitivity analysis incorporating broad-spectrum antibiotic use as an additional variable showed similar results (OR in a 1-day increase of steroid use, 1.05; 95%CI, 1.02–1.09).

Discussion

This study revealed an association between steroid use duration and fungal infections in patients with severe COVID-19 requiring MV. A day-long increase in steroid use showed a modest association with prolonged use of antifungal drug for ≥5 days, defined as fungal infection in this study, and this association remained consistent in two sensitivity analyses that adjusted for the definitions of fungal infection.

The pathophysiological reasons for these results can be explained with basic studies. Prolonged steroid use impairs the migration of macrophages and neutrophils to the infection site by decreasing or inhibiting the release of chemotactic factors. As the fact that the immune system against fungi includes phagocytosis by macrophages and cytotoxicity by polymorphonuclear leukocytes formed by chemotactic neutrophils is well known [17], steroids use might have contributed to prolonged use of antifungal drugs for clinically suspected invasive fungal infection. Moreover, dose- and duration-dependent immunosuppressive effects of steroids have been revealed in various studies [18–20], which could be shown as a risk increment by a 1-day increase in steroid use.

The observed odds ratio of 1.01 for each additional day of steroid use indicates a modest incremental risk (e.g., an OR of 1.1 for a 10-day increase). While the clinical implications should be carefully interpreted, even a small risk increment might still be clinically relevant because steroids are used more than often in severe COVID-19. While a 10-day use of dexamethasone for moderate-to-severe COVID-19 has been shown to decrease mortality [21], a prolonged regimen of steroids is still used worldwide [22, 23]. As increased susceptibility to fungal infections is associated with daily steroid use, only a validated regimen should be used. Furthermore, trial use of steroids for a few days should be avoided. In the current study, 327 of the 559 included patients (58%) and 16 of the 57 patients with fungal infection (28%) received steroids only for 5 days or less. As trial use of short-duration steroid regimens has now shown clinical benefits [24], physicians should be aware that fungal infections could occur even without long-term treatment.

It should be emphasized that microbiological proof of fungal infection with a positive culture of fungus was not available in this study and therefore the diagnosis unmet the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium consensus definitions of invasive fungal diseases. However, the fungal infection was defined as equal to or longer than 5 days of antifungal drug use, considering that antifungal drugs would highly likely be discontinued within 5 days when the fungal culture was negative [25, 26]. Therefore, the current study at least indicated that an increase in duration of steroid use was associated with prolonged antifungal drug administration with clinically suspected invasive fungal infection.

This study had some limitations. First, its retrospective design might have introduced biases due to unmeasured confounding factors, such as liver disease, post-transplant status, solid and/or hematological malignances, and several biomarkers including IL-6 and tumor necrosis factor α. Second, as microbiological, serological, and radiological data and autopsy findings for fungal infections are lacking, the association between longer duration of steroid use and higher risks for invasive fungal infection was not confirmed in the current study and should be validated with pathological data in another study. Third, the generalizability of our findings to recent COVID-19 subtypes might be limited, given the evolution of viral pathogenicity and the widespread implementation of vaccination programs. Future prospective studies incorporating cultural results should be conducted to obtain such information. Third, this study was conducted in 2020, during the early phases of the COVID-19 pandemic. Treatment protocols have evolved, potentially limiting the generalizability of our findings to the current practice. Replication with recent cohorts would help validate our results in the context of the current COVID-19 management strategies.

Conclusions

This study revealed an association between steroid use duration and prolonged antifungal drug uses for clinically suspected invasive fungal infections in patients with severe COVID-19 requiring MV. A daily increase in

steroid use was associated with prolonged use of antifungal medications for ≥ 5 days.

Abbreviations

CI	Confidence Interval
COVID-19	Coronavirus disease 2019
GEE	Generalized estimating equations
ICU	Intensive care unit
IL	Interleukin
IRB	Institutional Review Board
J-RECOVER	Japanese multicenter research of COVID-19 by assembling real-world data
MV	Mechanical ventilation
NYHA	New York Heart Association
OR	Odd ratio
RT-PCR	Reverse transcription polymerase chain reaction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10317-z.

Supplementary Material 1.

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Not applicable.

Authors' contributions
KM, RY, KM, DK, KH, KY, TT, MH, TO, AH, HY, and JS designed the study. RY, DK, and TT collected data. KY, MH, TO, AH, HY, and JS managed the quality control. KM, RY, TT, and EN performed the data analysis and interpretation. KM, RY, and JS wrote and critically revised the manuscript. All the authors have revised the manuscript accordingly. All the authors have read and approved the final version of the manuscript.

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Data availability
The data used in this study were obtained from the J-RECOVER study group. There were certain restrictions on access to data that were permitted for use in this study. These data are not publicly available but may be accessed upon reasonable request and with a license from the J-RECOVER study group.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Keio University School of Medicine (application number: 20200317) and conducted in accordance with the Declaration of Helsinki. The IRB decided that the requirement for informed consent was waived due to data anonymity.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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