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Rapid Communication

Effect of baricitinib in patients with coronavirus disease 2019 and respiratory failure: A propensity score-matched retrospective cohort study

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ABSTRACT

In this retrospective cohort study, we evaluated the efficacy of baricitinib in the treatment of coronavirus disease 2019 (COVID-19). Among 404 adult patients with COVID-19 who were admitted to our hospital between October 23, 2020, and July 31, 2021, 229 patients with respiratory failure were included. Among these, 41 patients in the baricitinib group and 41 patients in the control group were selected by propensity score matching to adjust for background factors. We compared the survival rates of the two groups at 30 and 60 days after admission. The 30-day survival rate was significantly higher in the baricitinib group than in the control group. However, there was no significant difference in 60-day survival in the two groups. Baricitinib may improve the early prognosis of patients with respiratory

Abbreviations: COVID-19, coronavirus disease 2019; DNI, Do Not Intubate; ECMO, Extracorporeal Membrane Oxygenation; eGFR, estimated glomerular filtration rate; JAK, Janus kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation.

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Janus kinase inhibitor
SARS-CoV-2
Survival

failure associated with COVID-19. However, efforts should be made to improve the long-term prognosis.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread worldwide. Cytokine storms are considered the major cause of coronavirus disease 2019 (COVID-19) exacerbation [1,2]; therefore, their suppression is expected to reduce COVID-19 severity.

Although only remdesivir and dexamethasone have previously been therapeutically indicated for patients with respiratory failure associated with COVID-19, the use of baricitinib for the treatment of COVID-19 in Japan was approved on April 23, 2021. Baricitinib, a Janus kinase (JAK) 1/2 inhibitor, is considered effective in COVID-19 owing to its strong anti-inflammatory [3] and antiviral effects; the latter is attributed to its ability to suppress SARS-CoV-2 endocytosis [4]. The results of a phase III trial of baricitinib against COVID-19 (COV-BARRIER) showed that adding baricitinib to standard therapy reduced mortality [5].

The objective of this retrospective cohort study was to evaluate the efficacy of baricitinib in the treatment of patients with respiratory failure associated with COVID-19 in Japan.

2. Patients and methods

The study protocol was approved by the Ethics Committee of the Hiroshima Prefectural Hospital (approval date: May 14, 2021; approval number: R3-5-3). The requirement for patient consent was waived owing to the retrospective design of the study and the use of data anonymization.

This study was conducted among adults (>18 years) with SARS-CoV-2 pneumonia at Hiroshima Prefectural Hospital in Hiroshima, Japan, between October 23, 2020 (the date when admission of patients with COVID-19 in our hospital was initiated again after being temporarily suspended), and July 31, 2021 (when none of the patients had received antibody medicines for COVID-19 or completed two doses of the COVID-19 vaccine). The data were extracted from electronic medical records. Survival at 30 and 60 days after admission was confirmed using electronic medical record information or by a telephone call to the patient.

The diagnosis of COVID-19 was confirmed by the presence of symptoms and/or contact with patients with COVID-19 and a positive SARS-CoV-2 genetic or qualitative antigen test.

Baricitinib was approved by the Ethics Committee of Hiroshima Prefectural Hospital for use in patients with respiratory failure associated with COVID-19, and its use was initiated on December 15, 2020. Except for initiation of baricitinib, there were no changes in the treatment protocol between October 23, 2020 (start of the study) and December 15, 2020. Baricitinib was subsequently approved for use in patients with respiratory failure associated with COVID-19 throughout Japan on April 23, 2021. As per the indications for baricitinib use, only patients with respiratory failure associated with COVID-19 were included in this study.

The following exclusion criteria were applied: death or transfer to another hospital within 3 days, treatment at other higher medical institutions and transfer to our hospital with improved condition, and history of advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/

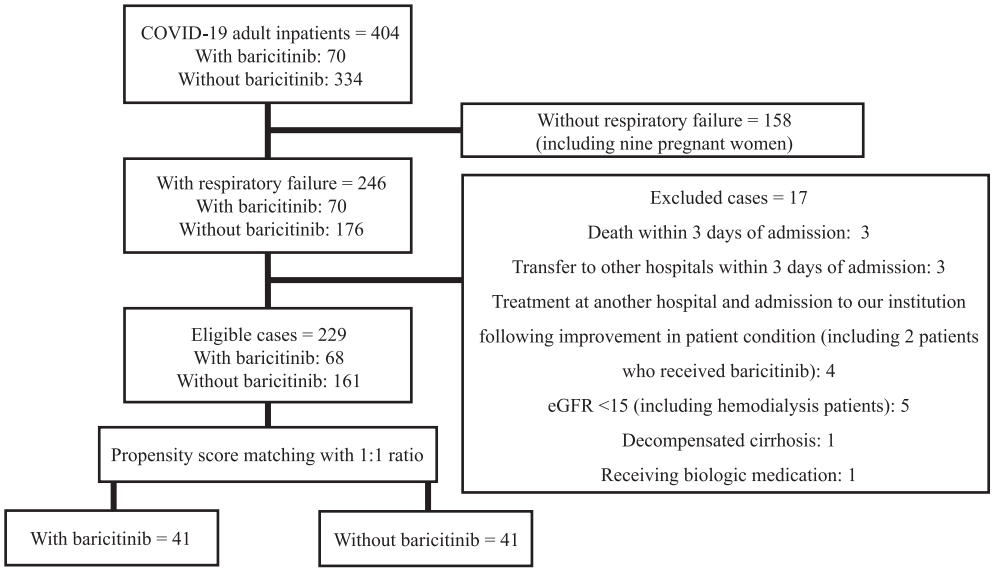

Fig. 1 – Flowchart of the patients included in the study. COVID-19, coronavirus disease; eGFR, estimated glomerular filtration rate.

Table 1 – Baseline characteristics of the baricitinib and control groups.

	Total cohort			Propensity score-matched cohort		
	Baricitinib group (n = 68)	Control group (n = 161)	p-Value	Baricitinib group (n = 41)	Control group (n = 41)	p-Value
Age	72 (57, 79)	69 (58, 78)	0.72	72 (57, 79)	67 (59, 76)	0.61
Sex, female	20 (29.4)	67 (41.6)	0.1	10 (24.4)	14 (34.1)	0.47
Body mass index			0.19			0.92
<20	0	10 (6.2)		0	0	
≥20 to <25	34 (50.0)	78 (48.4)		21 (51.2)	20 (48.8)	
≥25 to <30	24 (35.3)	52 (32.3)		12 (29.3)	14 (34.1)	
≥30	10 (14.7)	21 (13.0)		8 (19.5)	7 (17.1)	
Number of comorbidities			0.54			0.40
0	15 (22.1)	38 (23.6)		9 (22.0)	9 (23.7)	
1–2	35 (51.5)	91 (56.5)		20 (48.8)	25 (61.0)	
≥3	18 (26.5)	32 (19.9)		12 (29.3)	87 (17.1)	
Days from symptom onset to admission	5 (3, 8)	4 (2, 8)	0.06	5 (3, 8)	6 (2, 9)	0.70
Severity at admission			**0.001**			0.40
Mild	1 (1.5)	6 (3.7)		1 (2.4)	1 (2.4)	
Moderate I	11 (16.2)	44 (27.3)		8 (19.5)	6 (14.6)	
Moderate II	28 (41.2)	84 (52.2)		22 (53.7)	17 (41.5)	
Severe	28 (41.2)	27 (16.8)		10 (24.4)	17 (41.5)	
Do not intubate order	28 (41.2)	35 (21.7)	**0.004**	14 (34.1)	5 (12.2)	**0.04**
Other medications						
Favipiravir	49 (72.1)	106 (65.8)	0.44	33 (80.5)	24 (58.5)	0.05
Remdesivir	62 (91.2)	98 (60.9)	**<0.001**	35 (85.4)	35 (85.4)	1
Corticosteroids			**<0.001**			0.83
None	0	2 (1.2)		0	0	
Dexamethasone 6 or 6.6 mg	6 (8.8)	103 (64.0)		6 (14.6)	6 (14.6)	
Methylprednisolone 125 or 160 mg	6 (8.8)	19 (11.8)		6 (14.6)	4 (9.8)	
Methylprednisolone 500 or 1000 mg	56 (82.4)	37 (23.0)		29 (70.7)	31 (75.6)	
Tocilizumab	0	14 (8.7)	**0.01**	0	8 (19.5)	**0.005**
Heparin	43 (64.7)	70 (43.5)	**0.004**	24 (58.5)	27 (65.9)	0.65
Single-dose BNT162b2 mRNA COVID-19 vaccination	1 (1.5)	1 (0.6)	0.51	0	0	1

Categorical data are presented as numbers (percentages) and analyzed using Fisher's exact test or chi-square test. Continuous data are presented as median (first and third quartiles) and were analyzed using Mann-Whitney *U* test.
A p value < 0.05 (in boldface) was considered statistically significant.

min/1.73 m^2), decompensated cirrhosis, or administration of biologics or other JAK inhibitors.

Other than baricitinib, the following drugs were given in various combinations at the discretion of the attending physician: favipiravir (off-label use), corticosteroids (dexamethasone 6 mg or methylprednisolone 125–1000 mg, depending on symptoms), remdesivir, heparin, and tocilizumab (off-label use). Patients who received baricitinib (before April 23, 2021), favipiravir, and tocilizumab provided informed consent for off-label treatments.

The primary endpoint was the survival rate 30 and 60 days after admission. The propensity scores for treatment with baricitinib were calculated using a logistic regression model with the following covariates: age, sex, severity of disease at admission (Mild, Moderate I, Moderate II, and Severe), body mass index (grouped into four categories: <20, ≥20 to <25, ≥25 to <30, and ≥30), number of comorbidities at risk for severe disease (grouped into three categories: 0, 1–2, and ≥3), and if the patient was treated with or without favipiravir, remdesivir, and corticosteroid (grouped into four categories: none; dexamethasone, 6 or 6.6 mg; methylprednisolone, 125 or 160 mg; methylprednisolone, 500 or 1000 mg). The severity of COVID-19 infection was determined based on the official guidelines established by the Ministry of Health, Labor and Welfare of Japan [6]. In brief, "Mild" is defined as oxygen saturation (SpO_2) ≥96% and without shortness of breath; "Moderate I" is defined as 93% < SpO_2 < 96% or with shortness of breath or presence of pneumonia; "Moderate II" is defined as SpO_2 ≤93% or requirement of oxygen administration; "Severe" is defined as admission to the intensive care unit or requirement of mechanical ventilation. As some patients did not wish to be intubated or ventilated, we added the following to the definition of "Severe": SpO_2 <93% despite administration of >5 L/min oxygen by a nasal cannula or oxygen mask. The following diseases were considered comorbidities that are risk factors for severe disease: cancer, chronic kidney disease, chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease,

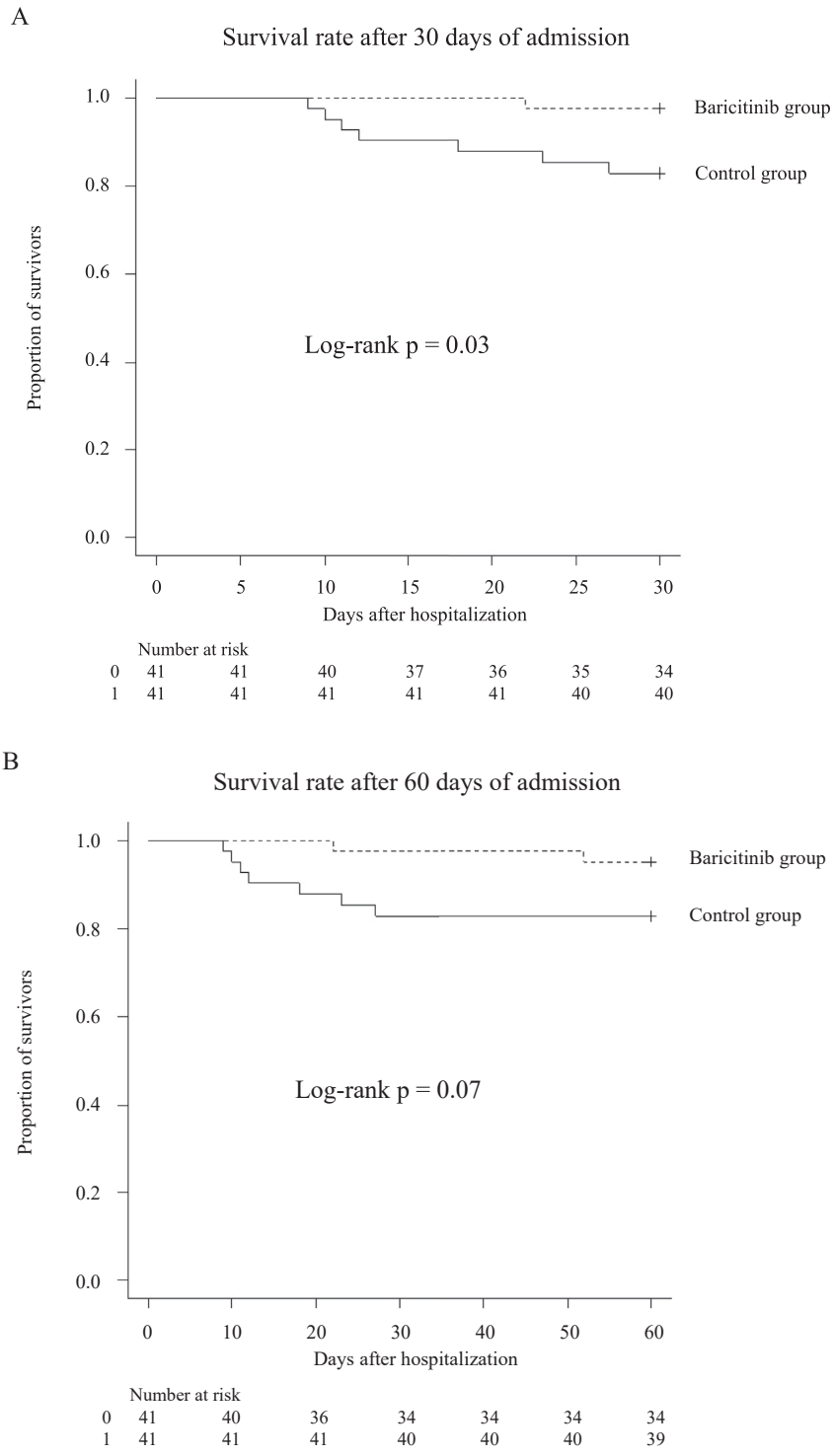

Fig. 2 – Kaplan-Meier survival curves for the two groups. (A) Survival rate after 30 days of admission. The difference in survival after 30 days of admission was significantly better in the baricitinib group than in the control group (p = 0.03). (B) Survival rate after 60 days of admission. There was no significant inter-group difference in survival rate after 60 days of admission (p = 0.07).

dementia, diabetes, heart diseases, hypertension, immunocompromised state, solid organ transplant, cerebrovascular disease, and dyslipidemia [7,8]. Based on these propensity scores, the baricitinib group was matched with the control group with a 1:1 nearest-neighbor algorithm using a caliper of 0.2 standard deviations.

Comparisons between the baricitinib and control groups were carried out using the Mann-Whitney *U* test for continuous variables and Fisher's exact test or chi-square test for categorical variables. A Kaplan-Meier method with log-rank test was used to evaluate differences in the survival rate between the baricitinib and control groups. All statistical

Table 2 – Clinical outcomes.

	Total cohort			Propensity score-matched cohort		
	Baricitinib group (n = 68)	Control group (n = 161)	p-Value	Baricitinib group (n = 41)	Control group (n = 41)	p-Value
Oxygen therapy at the most severe state			**<0.001**			**<0.001**
Nasal cannula	15 (22.1)	102 (63.4)		12 (29.3)	9 (22.0)	
Oxygen mask	1 (1.5)	5 (3.1)		1 (2.4)	0	
High-flow nasal cannula or non-invasive ventilation	38 (55.9)	19 (11.8)		20 (48.8)	5 (12.2)	
Mechanical ventilation	13 (19.1)	35 (21.7)		7 (17.1)	27 (65.9)	
Extracorporeal membrane oxygenation	1 (1.5)	0		1 (2.4)	0	
Outcome on release from isolation			0.11		0	**0.02**
Discharged to home (including via isolation facility)	31 (45.6)	92 (59.4)		23 (56.1)	13 (31.7)	
Rehabilitation transfer	29 (42.6)	45 (29.0)		14 (34.1)	19 (46.3)	
Worsened and transferred	2 (2.9)	4 (2.6)		1 (2.4)	2 (4.9)	
Released from isolation without improvement	3 (4.4)	2 (1.3)		2 (4.9)	0	
Death	3 (4.4)	12 (7.7)		1 (2.4)	7 (17.1)	
Infections						
Pneumonia	19 (27.9)	34 (21.1)	0.30	11 (26.8)	19 (46.3)	0.11
Urinary tract infection	7 (10.3)	6 (3.7)	0.10	4 (9.8)	1 (2.4)	0.40
Bacteremia	4 (5.9)	5 (3.1)	0.46	0	3 (7.3)	0.24
Aspergillus antigen or sputum culture positive	2 (2.9)	5 (3.1)	1	1 (2.4)	2 (4.9)	1
Cytomegalovirus antigenemia positive	10 (14.8)	0	**<0.001**	4 (9.8)	0	0.12
Nocardia pneumonia	1 (1.5)	0	0.30	1 (2.4)	0	1
Thromboembolism	5 (7.4)	0	**0.01**	3 (7.3)	0	0.24
Pulmonary embolism	1 (1.5)	0	0.31	1 (2.4)	0	1
Cerebral infarction	2 (2.9)	0	0.09	1 (2.4)	0	1
Deep venous thrombosis	3 (4.4)	0	**0.03**	1 (2.4)	0	1
Pneumothorax or pneumomediastinum	0	2 (1.2)	1	0	0	1
Liver dysfunction	14 (20.6)	31 (19.3)	0.96	9 (22)	10 (24.4)	1
Renal dysfunction	3 (4.4)	2 (1.2)	0.16	1 (2.4)	1 (2.4)	1

Liver dysfunction was defined as an increase in aspartate aminotransferase or alanine aminotransferase to at least twice the level prior to baricitinib administration and at least three times the upper limit of the reference values without other apparent causes.
Renal dysfunction was defined as an increase in creatinine to at least 1.5 times the level prior to baricitinib administration without other apparent causes.
Categorical data are presented as numbers (percentages) and analyzed using Fisher's exact test or chi-square test.
A p value < 0.05 (in boldface) was considered statistically significant.

analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [9], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Fig. 1 depicts the patient selection process. Propensity score matching was performed in 41 patients in both groups to reduce the differences in the characteristics between the two groups (Table 1). Despite reduced differences in the patient background, there were significant differences in the "do not intubate" (DNI) order and tocilizumab administration between the two groups.

The Kaplan-Meier survival curve is shown in Fig. 2A (30-day survival) and B (60-day survival). Log-rank test results showed significant differences in 30-day survival ($p = 0.03$), but there was no significant difference in survival at 60 days after admission ($p = 0.07$).

Table 2 shows the clinical course of the two groups. There were significant differences between the two groups in the method of oxygen administration at the time of maximum severity of the disease and in the outcome at the time of

release from isolation. No significant differences in adverse events were observed between the two groups.

4. Discussion

In this study, we showed that the survival rate at 30 days after admission was higher in the baricitinib group than in the control group. This is the first report of this finding in a real-world situation in Japan. In a phase III trial evaluating the efficacy of baricitinib (COV-BARRIER), mortality was lower in the baricitinib group at both 28 and 60 days after the date of randomization [5]. In this study, the reason for the lack of significant difference in survival at 60 days may partly be due to the small sample size but more likely because deaths after the 30th day were more common in the baricitinib group. Although baricitinib may reduce early mortality due to its anti-inflammatory effects, in some older adult patients who had severe pneumonia despite treatment with baricitinib, respiratory failure did not improve due to residual pneumonia or progressive fibrosis of the lung even after the acute phase was over, and death occurred. To prevent these cases, immunosuppressive therapy such as baricitinib, which also has antiviral effects, should be given from an early stage before pneumonia becomes severe or treatment to improve pulmonary fibrosis caused by prolonged severe pneumonia, such as administration of anti-fibrotic drugs, is necessary. In addition, baricitinib is contraindicated in patients with renal failure and pregnant women; therefore, a drug that can be administered to these patients is desirable.

Tocilizumab was used only in the control group, as it cannot be combined with baricitinib. Because of the small number of patients who received tocilizumab, its contribution to survival remains unknown. Further, whether the low number of patients requiring ventilation in the baricitinib group resulted from baricitinib administration is unclear, as it might have been due to the high number of DNI order cases. Although extracorporeal membrane oxygenation (ECMO) is not performed at our hospital, one patient in the baricitinib group underwent ECMO after being transferred to a higher medical institution.

No significant differences in adverse events were observed between the two groups. However, cytomegalovirus antigenemia positivity and thromboembolism were observed only in the baricitinib group among the participants in this study. The former may be related to the fact that the cytomegalovirus antigenemia assay was performed more aggressively in the baricitinib group, considering the risk of cytomegalovirus infection. Appropriate focus on the concomitant occurrence of infections is relevant because opportunistic infections such as cytomegalovirus infection may worsen the long-term prognosis in patients receiving baricitinib. With regard to the latter, two patients developed thromboembolism in the baricitinib group (four in the total cohort), and both developed thromboembolism despite receiving heparin, which reaffirms the need to monitor for thromboembolism while administering baricitinib.

The generalization of this study for future COVID-19 treatment is limited because it is a single-center study with a small sample size. Although we used propensity score matching to homogenize the differences between the groups in this study, it is impossible to homogenize all items.

Despite advancements in vaccinations and the availability of antibody medicines and oral antiviral medicines, patients may continue to experience severe illness due to the lack of early and appropriate treatment. Therefore, baricitinib is expected to contribute to COVID-19 treatment.

5. Conclusions

Baricitinib may improve early survival in patients with respiratory failure associated with COVID-19. However, efforts should be made to improve the long-term prognosis.

Author contribution

All authors meet the ICMJE authorship criteria. T Tanimoto, NI, and HM were involved in study conception and design; T Tanimoto, ST, SF, TH, MM, SI, SU, KH, NT, HH, TT, TO, TO, and SK were involved in data acquisition. All authors read and approved the final version of the manuscript.

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Conflict of Interest

The authors have no conflicts of interest.

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