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RESEARCH ARTICLE

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Combination therapy with remdesivir and immunomodulators improves respiratory status in COVID-19: A retrospective study

Yuichi Kojima[1] | Sho Nakakubo[1] | Keisuke Kamada[1,2,3] | Yu Yamashita[1,4] | Nozomu Takei[1] | Junichi Nakamura[1] | Munehiro Matsumoto[1] | Hiroshi Horii[1] | Kazuki Sato[1] | Hideki Shima[1] | Masaru Suzuki[1] | Satoshi Konno[1]

[1]Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2]Department of Mycobacterium Reference and Research, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, Japan

[3]Department of Epidemiology and Clinical Research, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, Japan

[4]Department of Respiratory Medicine 1, Obihiro Kosei General Hospital, Obihiro, Japan

Correspondence
Sho Nakakubo, Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan.
Email: shonakakubo@pop.med.hokudai.ac.jp

Abstract

Immunomodulators (tocilizumab/baricitinib) improve outcomes of coronavirus disease 2019 (COVID-19) patients, but the synergistic effect of remdesivir is unknown. The effect of combination therapy with remdesivir, immunomodulators, and standard treatment in COVID-19 patients was investigated. This retrospective, single-center study included COVID-19 patients who were treated with tocilizumab or baricitinib. The severity of respiratory status in the two groups on Days 14 and 28 and the duration to respiratory recovery in both groups were compared, and the effect of remdesivir use on respiratory status was examined in a multivariate analysis. Ninety-eight patients received tocilizumab or baricitinib; among them, 72 used remdesivir (remdesivir group) and 26 did not (control group). The remdesivir group achieved faster respiratory recovery than the control group (median 11 vs. 21 days, $p = 0.033$), faster weaning from supplemental oxygen (hazard ratio [HR]: 2.54, 95% confidence interval [CI]: 1.14–5.66, $p = 0.021$). Age, body mass index, diabetes mellitus, and time from onset to oxygen administration were independent prognostic factors. The remdesivir group achieved better severity level at Days 14 and 28 ($p = 0.033$ and 0.003, respectively) and greater improvement from baseline severity ($p = 0.047$ and 0.018, respectively). Remdesivir combination therapy did not prolong survival (HR: 0.31, 95% CI: 0.04–2.16, $p = 0.23$). Among severely ill COVID-19 patients who received immunomodulator, remdesivir contributed to a shorter respiratory recovery time and better respiratory status at Days 14 and 28. Concomitant remdesivir with immunomodulators and standard treatment may provide additional benefit in improving respiratory status of COVID-19 patients.

KEYWORDS

baricitinib, COVID-19, immunomodulator, remdesivir, retrospective study, tocilizumab

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and with the progression of the infection, the proliferating virus invades the lungs and other tissues, which induces a systemic cytokine storm.[1] COVID-19 causes pneumonia in severe cases, which frequently results in the need for prolonged oxygenation or ventilator use. Active research on the optimal treatment for COVID-19 that would allow early recovery of respiratory status in severe patients is being undertaken.

Remdesivir is a nucleotide prodrug of an adenosine analog that binds to the viral ribonucleic acid (RNA)-dependent RNA polymerase and inhibits viral replication by prematurely terminating RNA transcription.[2] Although remdesivir was initially developed to treat Ebola disease,[3] its therapeutic efficacy against COVID-19 has been tested for compassionate use.[4] There have been inconsistent findings regarding the clinical efficacy of remdesivir as a single agent against COVID-19 compared with standard care. Specifically, some randomized clinical trials (RCTs) have reported that remdesivir decreased the time to clinical recovery,[5,6] whereas other studies have reported contrasting results, with remdesivir failing to improve mortality.[7,8]

As studies have demonstrated the therapeutic effects of steroids on severely ill COVID-19 patients,[9,10] the research trend has shifted to the effectiveness of remdesivir in combination with standard treatment, including steroids. Several retrospective studies have reported the clinical benefits of using remdesivir in combination with steroids[11–13]; however, RCTs, including the DisCoVeRy trial, did not report a benefit of remdesivir in combination with standard therapy, including steroids, among severely ill COVID-19 patients.[14] Thus, the efficacy of remdesivir in combination with other treatments against COVID-19 remains unclear; however, patients in certain closed settings may benefit from combination therapy.

Tocilizumab, which is an anti-interleukin 6 monoclonal antibody,[15] and baricitinib, a Janus kinase inhibitor,[16] are the two major immunomodulators whose therapeutic efficacy for severe COVID-19 has been investigated. When used in combination with standard therapy, both agents have been demonstrated to reduce mortality in patients with severe COVID-19, especially those with high oxygen demand.[17–19] Although some of these studies used remdesivir, the contribution of remdesivir to the outcomes remains unclear. Two RCTs have reported the efficacy of tocilizumab in combination with remdesivir for severe COVID-19. However, both studies focused primarily on tocilizumab, as the comparisons were made with either remdesivir alone or steroid monotherapy.[20,21] It is unknown whether the combination of remdesivir provides additional benefit in patients using these immunomodulators. This study aimed to verify the clinical utility of using remdesivir in combination with immunomodulators among COVID-19 patients.

2 | METHODS

2.1 | Patients

This single-center, retrospective cohort study was approved by the Hokkaido University Hospital Division of Clinical Research Administration (Research Number 020-0107). COVID-19 patients admitted to the Hokkaido University Hospital between April 2020 and September 2021 and with polymerase chain reaction-based confirmation of SARS-CoV-2 infection were included. Patients treated with either tocilizumab or baricitinib, but not both, for COVID-19 were enrolled.

2.2 | Data collection

Demographics (age and sex) and clinical characteristics (body mass index [BMI], smoking history, vaccination history, comorbidities, respiratory status and severity, days from onset, treatment agents, laboratory data, and outcomes) were ascertained from medical records. The severity of COVID-19 was defined as follows: Level 1, hospitalized but not requiring supplemental oxygen; Level 2, hospitalized and requiring supplemental oxygen ≤4 L/min; Level 3, hospitalized and requiring oxygen therapy ≥5 L/min or receiving nasal high-flow oxygen therapy, nonrebreather, or noninvasive mechanical ventilation; Level 4, receiving invasive mechanical ventilation; and Level 5, dead.

The clinical endpoints were as follows: time to recovery of respiratory status, survival time within 28 days after immunomodulator administration, and respiratory status on 14 and 28 days after immunomodulator administration. The respiratory status was evaluated based on the severity level. The time to recovery of respiratory status was defined based on the duration (days) from the start to end of oxygen administration.

2.3 | Statistical analysis

Continuous and categorical data are expressed as median (interquartile range [IQR]) and proportions, respectively. Furthermore, continuous and categorical data were analyzed using the Wilcoxon rank-sum/Kruskal–Wallis tests and Pearson's χ^2/Fisher's exact tests, respectively. Factors influencing the time to respiratory recovery and survival time were analyzed using univariable and multiple Cox regression analysis, Kaplan–Meier analysis, and the logrank test. Significant variables ($p < 0.1$) in the univariate analysis and clinically significant items (sex, BMI, chronic kidney disease, diabetes mellitus, and respiratory severity at the time of immunomodulator administration) were included in the multivariate models. Fisher's exact test and Wilcoxon rank-sum test were used to test the respiratory status that was evaluated on Days 14 and 28. Additionally, sensitivity analyses were performed to examine the robustness of the findings. For sensitivity analysis, propensity scores were calculated through

logistic regression and used as matching parameters to adjust for measured confounders. Patients with and without remdesivir treatment were matched 1:1 using nearest neighbor matching with a caliper of 0.25. All *p*-values were two-tailed. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using JMP (SAS Institute Inc.).

3 | RESULTS

3.1 | Study population

During the study period, 459 patients with COVID-19 were admitted to the study center; among them, 100 patients received tocilizumab or baricitinib for COVID-19. Two patients who were initially treated with baricitinib but were subsequently switched to tocilizumab were excluded. Among the remaining 98 patients, 72 patients were treated with remdesivir (combination group) while 26 were not (control group), and two patients with insufficient clinical information to determine the respiratory recovery and one patient who underwent home oxygen therapy due to lung disease were excluded from the analysis of respiratory recovery (Figure 1).

3.2 | Characteristics

The median age of all 98 patients was 60.5 years; moreover, 74.5% of the patients were male. Compared with the control group ($n = 26$), the combination group ($n = 72$) had a higher BMI (27.1 vs. 23.9, $p = 0.044$), lower prevalence of chronic kidney disease (2.8% vs. 15.4%, $p = 0.022$), and lower frequency of tocilizumab use (43.1% vs. 88.5%, $p = 0.004$). There were no significant between-group differences in age; sex ratio; and prevalence of smoking history, immunosuppressive drug use, obesity, chronic heart disease, diabetes mellitus, collagen disease, hypertension, and respiratory disease. Only one patient in the control group received vaccination twice against SARS-CoV-2. There was no significant between-group difference in the days from the onset of illness to the oxygen administration; however, it tended to be shorter in the combination group than in the control group (median 7 vs. 8, $p = 0.079$; Table 1). Compared with the

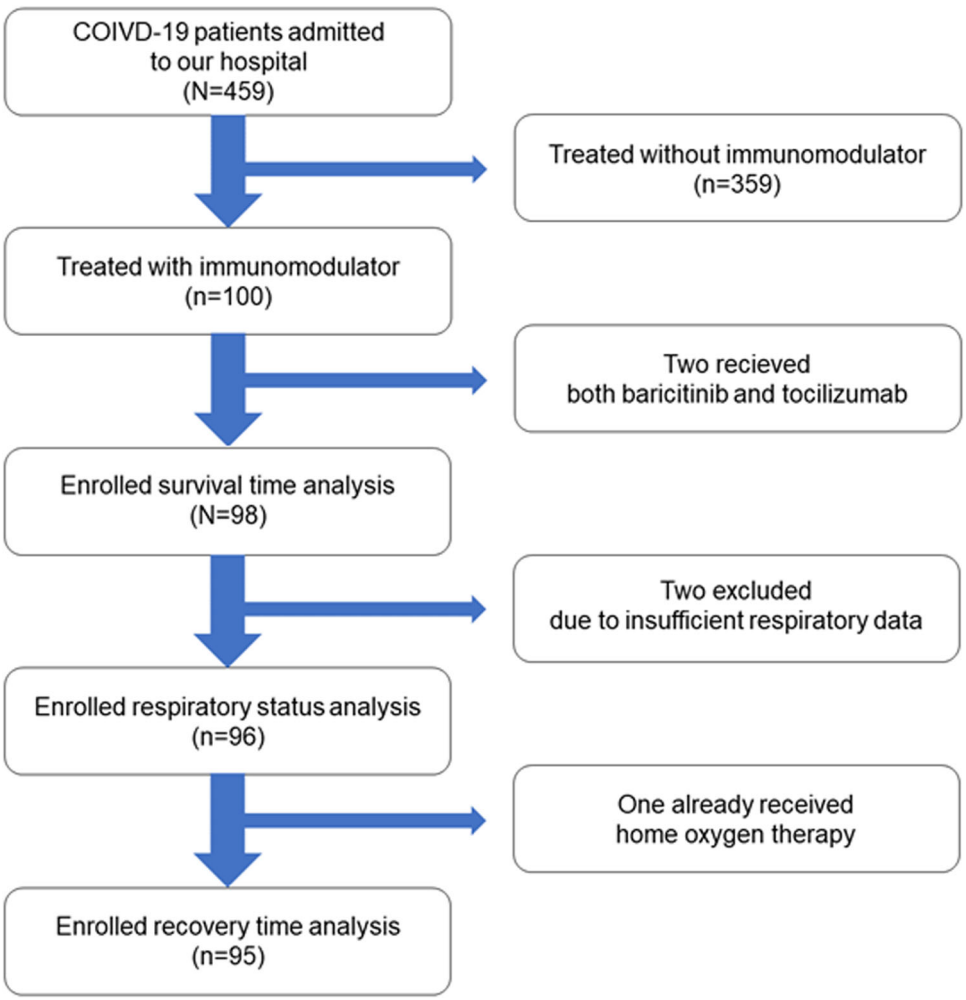

FIGURE 1 Flowchart of participant selection. COVID-19, coronavirus disease 2019.

TABLE 1 Baseline characteristics of the remdesivir combination group and control group

Characteristics	Study cohort, *N* = 98	Combination group (with remdesivir) *N* = 72	Control group (without remdesivir) *N* = 26	*p*-value
Age (years)	60.5 (54.0–70.3)	60.0 (54.0–69.0)	65.0 (55.0–71.0)	0.23
Sex (male)	73 (74.5)	56 (77.8)	17 (65.4)	0.21
Current smoker	16 (16.3)	15 (20.8)	1 (4.0)	0.051
BMI (kg/m^2)[a]	26.5 (23.4–30.1)	27.1 (24.2–30.1)	23.9 (21.1–29.0)	0.044
Chronic heart disease	17 (17.4)	11 (15.3)	6 (23.1)	0.37
Chronic kidney disease	6 (6.1)	2 (2.8)	4 (15.4)	0.022
Diabetes mellitus	36 (36.7)	26 (36.1)	10 (38.5)	0.83
Any collagen disease	3 (3.1)	2 (2.8)	1 (3.9)	0.79
Hypertension	46 (46.9)	37 (51.4)	9 (34.6)	0.14
Any respiratory disease	8 (8.1)	5 (6.9)	3 (11.5)	0.46
Regular immunosuppressive drug use	3 (3.1)	2 (2.8)	1 (3.9)	0.79
Vaccination twice	1 (1.0)	0 (0)	1 (3.9)	0.09
Time from onset to supplemental oxygen administration (days)[b]	7 (6–10)	7 (6–9)	8 (6–10)	0.079
Time from onset to immunomodulator administration (days)[c]	9 (7–12)	9 (7–11)	11.5 (9.8–14)	<0.001
Time from onset to remdesivir administration (day)		7 (6–9)		
Time from remdesivir to immunomodulator administration (day)		1 (0–2)		
Treatment				
Steroid	96 (98.0)	71 (98.6)	26 (96.3)	0.55
Heparin	78 (79.6)	60 (83.3)	19 (73.1)	0.26
Tocilizumab	64 (65.3)	41 (56.9)	23 (88.5)	0.004
Baricitinib	34 (34.7)	31 (43.1)	3 (11.5)	0.004
Antibody combination casirivimab/imdevimab	1 (1.0)	0 (0)	1 (1.4)	0.55
Blood test at administration				
White blood cell (/μl)	7900 (5550–10825)	7465 (5225–10675)	9150 (6875–11275)	0.11
Neutrophils (/μl)[d]	6991 (4465–9755)	6090 (4294–9666)	8736 (6102–9956)	0.073
Lymphocytes (/μl)[d]	611 (476–908)	647 (487–907)	592 (370–911)	0.33
Eosinophil (/μl)[d]	0 (0)	0 (0)	0 (0)	0.81
Hemoglobin (g/dl)	14.2 (12.9–15.0)	14.4 (13.2–15.1)	13.5 (12.2–14.9)	0.045
Platelet ($\times 10^4$/μl)	19.0 (13.4–25.9)	19.9 (13.9–26.3)	18.0 (12.6–23.8)	0.34
LDH (U/L)	512.5 (419.8–647.5)	518 (413–626)	518 (440–713)	0.41
CRP (mg/ml)	7.1 (3.6–11.2)	7.4 (3.5–11.3)	5.6 (3.6–11.2)	0.50
KL-6 (U/ml)[e]	402 (289.5–617.5)	372 (286–543)	444 (377–855)	0.33
Procalcitonin (ng/ml)[f]	0.08 (0.05–0.15)	0.08 (0.05–0.18)	0.08 (0.05–0.09)	0.34
Ferritin (ng/ml)[g]	1125.5 (693.8–1924.5)	1090 (697–1889)	1366 (673–2118)	0.81
D-dimer (μg/ml)[h]	1.4 (1.0–2.5)	1.4 (0.9–2.1)	1.5 (1.2–7.0)	0.030

TABLE 1 (Continued)

Characteristics	Study cohort, *N* = 98	Combination group (with remdesivir) *N* = 72	Control group (without remdesivir) *N* = 26	*p*-value
Severity				
1	1 (1.0)	1 (1.4)	0 (0)	
2	9 (9.2)	8 (11.1)	1 (3.7)	
3	76 (77.6)	56 (77.8)	20 (76.9)	
4	12 (12.2)	7 (9.7)	5 (19.2)	0.41

Note: Data are shown as median (interquartile range) or number (%).

COVID-19 disease severity upon was categorized as: Level 1, hospitalized but not requiring supplemental oxygen; Level 2, hospitalized and requiring ≤4 L/min supplemental oxygen; Level 3, hospitalized and requiring ≥5 L/min supplemental oxygen or receiving nasal high-flow oxygen therapy, nonrebreather, or noninvasive mechanical ventilation; and Level 4, receiving invasive mechanical ventilation.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase.

[a]*N* = 92.

[b]*N* = 97.

[c]*N* = "Immunomodulators" refers to tocilizumab and baricitinib.

[d]*N* = 94.

[e]*N* = 69.

[f]*N* = 60.

[g]*N* = 70.

[h]*N* = 95.

control group, the combination group showed a longer time from disease onset to immunomodulator administration (median: 9 vs. 11.5 days, $p < 0.001$). In the combination group, remdesivir was administered at a median of 7 days (IQR: 6–9 days) after onset; additionally, most patients received remdesivir concomitantly or before immunomodulator administration (median 1 day, IQR: 0–2). Most patients received steroid treatment for COVID-19 (98.6% and 96.3% in the combination and control groups, respectively; Table 1). With regard to blood tests, the combination group had lower D-dimer levels (1.4 vs. 1.5, $p = 0.030$) and higher hemoglobin levels (14.4 vs. 13.5, $p = 0.045$) than the control group. There was no significant between-group difference in COVID-19 severity at the start of immunomodulator administration, with 77.8% and 76.9% of patients in the combination and control groups, respectively, showing severity level 3 or higher (Table 1).

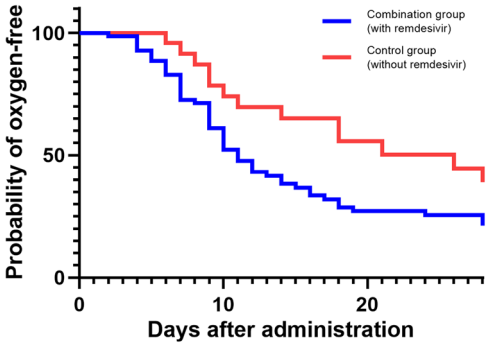

FIGURE 2 Differences in the Kaplan–Meier estimates of time to recovery of respiratory status between the remdesivir combination group and the control group. Recovery of respiratory status was defined as not requiring supplemental oxygen administration.

3.3 | Time to recovery of respiratory status

Kaplan–Meier curve analysis revealed that compared with the control group, the combination group achieved faster recovery, with the logrank test revealing a significant between-group difference (median time to oxygen-free status: 11 vs. 21 days, $p = 0.033$) (Figure 2). Among patients treated with an immunomodulator, univariate analysis revealed that the use of remdesivir was associated with a significantly shorter time to recovery of respiratory status. Moreover, lower age, absence of chronic heart disease, and late immunomodulator administration were significantly associated with shorter time to recovery of respiratory status (Table 2). Additionally, multivariate analysis revealed that remdesivir use (hazard ratio [HR]: 2.54, 95% confidence interval [CI]: 1.14–5.66, $p = 0.021$), lower age (HR: 0.96, 95% CI: 0.93–0.99, $p = 0.003$), lower BMI (HR: 0.94, 95% CI: 0.89–0.99, $p = 0.032$), and diabetes mellitus (HR: 1.92, 95% CI: 1.05–3.51, $p = 0.033$) were independently associated with early recovery of respiratory status. Using severity level 1 or 2 as a reference, severity levels 3 and 4 at immunomodulator initiation were risk factors for delayed respiratory condition recovery (HR: 0.37, 95% CI: 0.15–0.96, $p = 0.041$ and HR: 0.16, 95% CI: 0.04–0.65, $p = 0.010$, respectively; Table 2).

TABLE 2 Cox regression analysis of predictive factors for recovery of respiratory status among patients in the remdesivir combination group and in the control group

Factors	Univariate analysis HR (95% CI)	*p*-value	Multivariate analysis HR (95% CI)	*p*-value
Age (years)	0.97 (0.95–0.99)	0.003	0.96 (0.93–0.99)	0.003
Sex (male)	0.81 (0.46–1.43)	0.47	1.04 (0.53–2.03)	0.92
Current smoker	1.57 (0.85–2.89)	0.15		
BMI (kg/m^2)	0.91 (0.29–3.46)	0.90	0.94 (0.89–0.99)	0.032
Chronic heart disease	0.32 (0.14–0.75)	0.008	0.49 (0.19–1.23)	0.13
Chronic kidney disease	0.47 (0.11–1.92)	0.29	0.30 (0.05–1.68)	0.17
Diabetes mellitus	1.17 (0.71–1.92)	0.55	1.92 (1.05–3.51)	0.033
Any collagen disease	0.55 (0.08–4.00)	0.56		
Hypertension	0.49 (0.29–0.81)	0.005	0.63 (0.35–1.15)	0.13
Any respiratory disease	1.18 (0.47–2.94)	0.73		
Regular use of immunosuppressive drug	1.27 (0.31–5.20)	0.74		
Time from onset to immunomodulator administration (days)[a]	1.02 (0.95–1.10)	0.58	1.10 (0.99–1.23)	0.069
Time from remdesivir use to immunomodulator administration (days)	0.87 (0.22–2.85)	0.83		
Heparin	0.93 (0.51–1.69)	0.81		
Remdesivir use	1.88 (1.02–3.46)	0.041	2.54 (1.14–5.66)	0.021
Tocilizumab use	0.63 (0.38–1.02)	0.062	1.09 (0.62–1.90)	0.76
Baricitinib use	1.60 (0.98–2.61)	0.062		
Blood test at administration				
White blood cell (per 10^3/μl)	0.15 (0.0005–1.97)	0.33		
Neutrophils (per 10^3/μl)	0.98 (0.91–1.05)	0.59		
Lymphocytes (per 10^2/μl)	1.05 (0.98–1.12)	0.15		
Eosinophils (/μl)	1.00 (0.99–1.01)	0.51		
Hemoglobin (per 10 g/dl)	2.80 (0.75–9.90)	0.12		
Platelets (per 10^5/μl)	1.20 (0.95–1.50)	0.12		
LDH (per 10^2 U/L)	0.93 (0.79–1.08)	0.33		
CRP (mg/ml)	1.00 (0.96–1.05)	0.93		
KL-6 (per 10^2 U/ml)	0.92 (0.82–1.01)	0.12		
Ferritin (per 10^3 ng/ml)	1.00 (0.98–1.02)	0.92		
D-dimer (μg/ml)	0.98 (0.95–1.00)	0.17		
Severity level				
1 or 2	(Reference)	(Reference)	(Reference)	(Reference)
3	0.53 (0.26–1.09)	0.083	0.37 (0.15–0.96)	0.041
4	0.20 (0.06–0.67)	0.008	0.16 (0.04–0.65)	0.010

Note: COVID-19 disease severity was categorized as: Level 1, hospitalized but not requiring supplemental oxygen; Level 2, hospitalized and requiring ≤4 L/min supplemental oxygen; Level 3, hospitalized and requiring ≥5 L/min supplemental oxygen or receiving nasal high-flow oxygen therapy, nonrebreather, or noninvasive mechanical ventilation; and Level 4, receiving invasive mechanical ventilation.

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HR, hazard ratio; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase.

[a]"Immunomodulators" refers to tocilizumab and baricitinib.

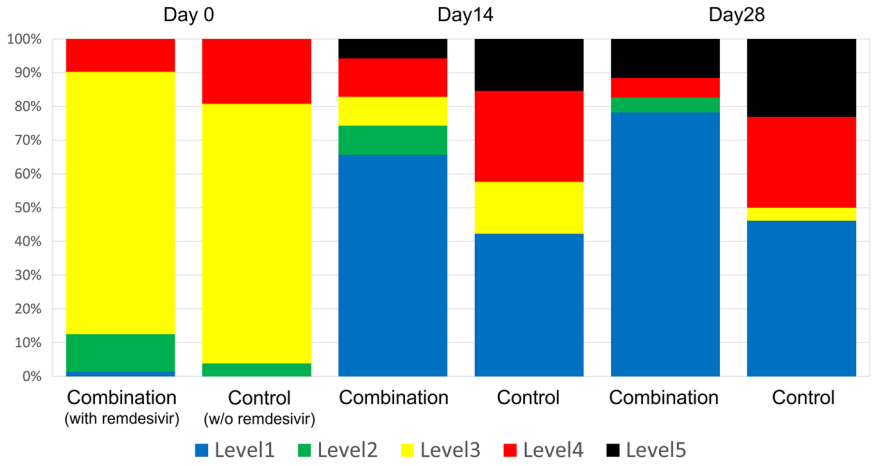

FIGURE 3 Respiratory status severity according to duration (days) after immunomodulator administration in the remdesivir combination group and the control group. Respiratory status severity was categorized as: Level 1, hospitalized but not requiring supplemental oxygen; Level 2, hospitalized and requiring ≤4 L/min supplemental oxygen; Level 3, hospitalized and requiring ≥5 L/min supplemental oxygen or receiving nasal high-flow oxygen therapy, nonrebreather, or noninvasive mechanical ventilation; and Level 4, receiving invasive mechanical ventilation.

As a subgroup analysis, we performed a multivariate analysis restricted to the group of patients using remdesivir ($N = 70$). We found that tocilizumab use was not significantly associated with improved respiratory status compared to baricitinib use (HR: 1.13, 95% CI: 0.62–2.06, $p = 0.69$) (Supporting Information: Table 1). Also, we examined the factors contributing to the time to recovery of respiratory status for patients treated with tocilizumab ($N = 63$) and for those treated with baricitinib ($N = 33$). Cox regression multivariate analysis showed that the use of remdesivir was significantly associated with faster recovery of respiratory status in the tocilizumab group (HR: 3.02, 95% CI: 1.08–8.40, $p = 0.034$), but not in the baricitinib group (HR: 1.55, 95% CI: 0.35–6.79, $p = 0.56$) (Supporting Information: Table 2).

3.4 | Respiratory status on Days 14 and 28 after immunomodulator administration

Figure 3 shows the percentage of each severity level at immunomodulator initiation, as well as after 14 and 28 days. Compared with the control group, the combination group had significantly lower severity levels at Days 14 and 28 ($p = 0.033$, $p = 0.003$, respectively). Regarding the degree of change from the baseline severity level (at Day 0), the combination group showed a significantly greater change than the control group at Days 14 and 28 (Day 14; median −2 vs. 0, $p = 0.047$, Day 28; median −2 vs. 0, $p = 0.018$, respectively), which indicated a more pronounced recovery of respiratory status in the combination group.

3.5 | Survival

Kaplan–Meier curve analysis revealed significant between-group differences in the survival curves ($p = 0.028$; Supporting Information: Figure 1). Furthermore, univariate Cox regression analysis revealed that factors that significantly contributed to increased survival time were remdesivir use, low age, absence of chronic kidney disease, late immunomodulator administration, baricitinib use, and high hemoglobin levels (Table 3). However, in the multivariate analysis, remdesivir use was not a significant contributing factor (HR: 0.31, 95% CI: 0.04–2.16, $p = 0.23$), whereas lower age (HR: 1.12, 95% CI: 1.02–1.24, $p = 0.022$), male sex (HR: 0.17, 95% CI: 0.03–0.98, $p = 0.047$), and absence of chronic kidney disease (HR: 87.91, 95% CI: 4.43–1743.44, $p = 0.003$) were independent contributory factors. Severe respiratory status at immunomodulator initiation was a risk factor for poor prognosis (severity level 3: HR: 30.88, 95% CI: 1.60–596.05, $p = 0.023$ and Level 4: HR: 34.92, 95% CI: 1.21–1010.09, $p = 0.039$; Table 3).

3.6 | Sensitivity analyses

Between-group matching of confounders, including age, BMI, presence of chronic kidney disease, and time from onset to immunomodulator administration, was performed. After propensity score matching, the study population comprised 20 remdesivir users and 20 remdesivir nonusers (Supporting Information: Table 3). Compared with the control group, the combination group showed faster recovery of respiratory status ($p = 0.006$; Supporting Information: Figure 2). Moreover, the combination group showed a nonsignificantly longer survival than the control group ($p = 0.087$; Supporting Information: Figure 3). Although the combination group had a higher proportion of better respiratory status on Days 14 and 28 compared with the control group, the difference was not statistically significant. ($p = 0.141$ and 0.070, respectively; Supporting Information: Figure 4). Regarding the

TABLE 3 Cox regression analysis of predictive factors for improvement in survival time among patients in the combination or control group

Factors	Univariate analysis HR (95% CI)	*p*-value	Multivariate analysis HR (95% CI)	*p*-value
Age (years)	1.08 (1.09–1.15)	0.001	1.12 (1.02–1.24)	0.022
Sex (male)	0.59 (0.22–1.59)	0.30	0.17 (0.03–0.98)	0.047
Current smoker	0.30 (0.04–2.25)	0.24		
BMI (kg/m^2)	0.97 (0.87–1.05)	0.49	1.12 (0.95–1.31)	0.17
Chronic heart disease	2.13 (0.75–6.04)	0.16	0.52 (0.11–2.37)	0.40
Chronic kidney disease	7.39 (2.39–22.84)	0.0005	87.91 (4.43–1743.44)	0.003
Diabetes mellitus	0.96 (0.35–2.58)	0.93	0.37 (0.08–1.71)	0.37
Any collagen disease	2.68 (0.36–20.21)	0.34		
Hypertension	2.83 (0.99–8.02)	0.051	3.49 (0.49–24.85)	0.21
Any respiratory disease	3.01 (0.86–10.50)	0.084		
Regular use of immunosuppressive drug	2.68 (0.36–20.21)	0.34		
Time from onset to immunomodulator administration (days)[a]	0.83 (0.71–0.97)	0.021	0.75 (0.57–1.00)	0.054
Time from remdesivir administration to immunomodulator administration (days)	0.89 (0.48–1.40)	0.67		
Heparin	0.80 (0.26–2.45)	0.70		
Remdesivir use	0.36 (0.14–0.93)	0.036	0.31 (0.04–2.16)	0.23
Tocilizumab use	9.63 (1.28–72.66)	0.028	3.43 (0.34–34.17)	0.29
Baricitinib use	0.10 (0.01–0.78)	0.028		
Blood test at administration				
White blood cell (per $10^3/\mu l$)	0.97 (0.84–1.02)	0.62		
Neutrophils (per $10^3/\mu l$)	1.03 (0.89–1.19)	0.65		
Lymphocytes (per $10^2/\mu l$)	0.90 (0.74–1.06)	0.27		
Eosinophils ($/\mu l$)	0.99 (0.92–1.01)	0.61		
Hemoglobin (per 10 g/dl)	0.03 (0.002–0.48)	0.011	14.53 (0.25–837.65)	0.2
Platelets (per $10^5/\mu l$)	0.69 (0.42–1.14)	0.15		
LDH (per 10^2 U/L)	1.21 (0.94–1.52)	0.11		
CRP (mg/ml)	1.01 (0.92–1.10)	0.93		
KL-6 (per 10^2 U/ml)	1.12 (0.94–1.26)	0.12		
Ferritin (per 10^3 ng/ml)	0.95 (0.85–1.03)	0.34		
D-dimer (μg/ml)	1.01 (0.99–1.02)	0.26		
Severity level				
1 or 2	(Reference)	(Reference)	(Reference)	(Reference)
3	1.69 (0.22–13.03)	0.61	30.88 (1.60–596.05)	0.023
4	3.65 (0.41–32.69)	0.25	34.92 (1.21–1010.09)	0.039

Note: COVID-19 disease severity upon was categorized as: Level 1, hospitalized but not requiring supplemental oxygen; Level 2, hospitalized and requiring ≤4 L/min supplemental oxygen; Level 3, hospitalized and requiring ≥5 L/min supplemental oxygen or receiving nasal high-flow oxygen therapy, nonrebreather, or noninvasive mechanical ventilation; and Level 4, receiving invasive mechanical ventilation.

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HR, hazard ratio; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase.

[a]"Immunomodulators" refers to tocilizumab and baricitinib.

change of severity level from baseline, the combination group showed a nonsignificantly greater change than the control group at Days 14 and 28 (Day 14; median −2 vs. 0, $p = 0.070$, Day 28; median −2 vs. −2, $p = 0.052$, respectively).

4 | DISCUSSION

The characteristics of COVID-19 patients treated with immunomodulators and either with or without remdesivir were evaluated. Multivariate analysis revealed that remdesivir use did not yield a favorable survival outcome; however, remdesivir use significantly contributed to early respiratory recovery and an increased rate of improved respiratory status at Days 14 and 28. Although the sensitivity analysis yielded a limited number of matched cases, the findings demonstrated the efficacy of remdesivir. Subgroup analysis suggested no difference in clinical outcomes between tocilizumab and baricitinib among remdesivir users. The results of our study indicate that the combination of remdesivir may provide additional benefit in patients using tocilizumab or baricitinib.

The observed efficacy of remdesivir suggests that its antiviral effect is closely associated with the recovery of respiratory status. There are concerns that the use of immunomodulators among COVID-19 patients may delay viral clearance from the host.[22,23] An in vivo study reported that the viral load was increased and decreased by steroid use and remdesivir combination use, respectively[24]; however, further studies are warranted. Immunomodulators exert significant benefits in severely ill COVID-19 patients by suppressing inflammatory cytokines.[17,25] Remdesivir may provide additional therapeutic benefits by effectively suppressing viral replication, which could be increased by immunomodulator use.

The respiratory status during remdesivir administration may influence the outcomes of patients with COVID-19. Specifically, a subgroup analysis of the ACTT-1 study[5] and DisCoVeRy trial[14] showed that remdesivir use significantly delayed the requirement for a new ventilator or extracorporeal membrane oxygenation, as well as death, in patients without high oxygen demand during drug administration. In this study, there was no between-group difference in the severity of COVID-19 at immunomodulator initiation. In the study center, COVID-19 patients who required supplemental oxygen administration were usually treated with steroids, and immunomodulators were administered to patients with increased oxygen demand according to the treatment guideline.[26,27]

A strength of this study is that the baseline treatment and respiratory status were well matched for both groups. However, there were between-group differences in some background characteristics. To avoid accumulation of toxic substances, remdesivir is not recommended for patients with renal impairment (estimated glomerular filtration rate <30 ml/min) since it may cause hepatic and renal toxicity.[28] Moreover, baricitinib use has not been sufficiently evaluated in these patients. This could explain why the combination group had fewer patients with chronic kidney disease than the control group and more patients used tocilizumab. Accordingly, chronic kidney disease, despite not being a significant variable in the univariate analysis, was included in the multivariate analysis. Even after adjusting for confounding factors, remdesivir use was significantly associated with faster recovery of respiratory status.

Compared with the combination group, the control group received immunomodulators relatively later, following an increase in oxygen demand. Patients with relatively late-onset respiratory deterioration may have often not received remdesivir since it is not expected to be effective in the later phase of COVID-19. In patients with severe COVID-19, remdesivir has been shown to lack a therapeutic effect at >7 days after onset.[6,14] Moreover, given that early remdesivir administration (within 5–7 days after onset) in patients with mild COVID-19 is highly effective in preventing severe disease,[29,30] early remdesivir administration seems essential. Contrastingly, multivariate analysis showed that the timing of immunomodulator initiation had a limited effect on improving respiratory status or death. Among patients who received immunomodulators, remdesivir was administered relatively late (median of 7 days [IQR: 6–9] after onset). This suggests that for patients receiving immunomodulators, the timing of remdesivir administration after COVID-19 onset is not a limiting factor.

This study has several limitations. First, this was a retrospective study; therefore, prospective studies are warranted to confirm the clinical benefit of adding remdesivir to patients using immunomodulators. Second, although the overall analysis was able to demonstrate the benefit of remdesivir combination, the subgroup analysis results did not reach statistical significance in the baricitinib use group. This may be related to the small number of patients who did not use remdesivir in the baricitinib group ($n = 3$). Lastly, due to missing data, variant SARS-CoV-2 strains and changes in healthcare availability, which may affect patient outcomes, were not investigated.

5 | CONCLUSION

Compared with the control group, the combination group had a shorter time to recovery of respiratory status and a higher improvement rate at Days 14 and 28. The findings indicate the potential benefits of remdesivir as adjunctive therapy in COVID-19 patients receiving immunomodulators and standard treatment, although these benefits need to be confirmed in future prospective studies.

AUTHOR CONTRIBUTIONS

Yuichi Kojima and Sho Nakakubo contributed to the study conception, design, interpretation of results, statistical analysis, and writing of the manuscript. Keisuke Kamada, Yu Yamashita, Nozomu Takei, Junichi Nakamura, Munehiro Matsumoto, Hiroshi Horii, Kazuki Sato, and Hideki Shima contributed to the acquisition and interpretation of data. Nozomu Takei contributed to statistical analysis. Yuichi Kojima, Sho Nakakubo, and Munehiro Matsumoto contributed to data acquisition. Masaru Suzuki and Satoshi Konno contributed to the study conception and design, data acquisition and interpretation of

results, and review of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The research protocol was approved by the Ethics Committee of the Hokkaido University Hospital (Research No. 020-0107). The analyses were conducted using existing samples collected in the course of routine clinical practice, with no additional risks to the patients. Therefore, the requirement for obtaining an individual participants' informed consent was waived by the above ethics committee. All methods were carried out in accordance with relevant guidelines and regulations of the Ethics Committee of the Hokkaido University Hospital. Informed consent for study participation was officially announced on the website. All patient data were anonymized.

ORCID

Sho Nakakubo http://orcid.org/0000-0003-1560-8361

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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