

Effectiveness of remdesivir in patients with COVID-19 and severe renal insufficiency: a nationwide cohort study in Japan

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ABSTRACT

Background: The effectiveness of remdesivir in patients with coronavirus disease 2019 (COVID-19) and severe renal insufficiency remains underexplored.

Objectives: To evaluate whether remdesivir reduces the risk of mortality or invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) in this population.

Methods: This retrospective observational study utilizing the COVID-19 Registry Japan (COVIREGI-JP) included noncritical patients with COVID-19 and severe renal insufficiency (defined as serum creatinine levels ≥ 3 mg/dL, on maintenance dialysis, or kidney transplant recipients) admitted to Japanese hospitals within 7 days of symptom onset between January 1, 2020, and May 8, 2023. Patients were classified into the remdesivir group if remdesivir was initiated within the first 2 days of admission. We estimated the multivariable-adjusted hazard ratio (HR) for mortality and initiation of IMV/ECMO using landmark analysis to address immortal time bias.

Results: Among the 1,449 patients included in the landmark analysis (median age, 74 years [interquartile range 62–84 years]; 992 [68.5%] were male), 272 initiated remdesivir within the first 2 days of admission. During the 28 days from the landmark timepoint, 19 (7.0%) and 136 (11.6%) patients in the remdesivir and control groups, respectively, had an outcome. The remdesivir group had a lower risk of mortality or IMV/ECMO initiation than the control group (adjusted HR, 0.44; 95% confidence interval, 0.23–0.83).

Conclusions: In noncritical patients with COVID-19 and severe renal insufficiency at admission, initiating remdesivir early after disease onset, within the first 2 days of admission, led to a lower risk of mortality or IMV/ECMO initiation, compared with non-initiation of remdesivir.

INTRODUCTION

According to the World Health Organization (WHO), as of March 2024, coronavirus disease 2019 (COVID-19) had resulted in 7 million deaths [1]. Effective vaccines have become widely available. However, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged, along with breakthrough infections due to decreasing vaccine efficacy over time [2]. Thus, antiviral agents remain an important tool against COVID-19, especially in high-risk patients. The antiviral agent remdesivir has shown effectiveness in meta-analyses as a treatment for COVID-19 [3]. Remdesivir is indicated for patients with COVID-19 who are non-hospitalized and at high risk of progression to severe disease; hospitalized, at high risk of progression to severe disease, and do not require supplemental oxygen; and hospitalized and require low-flow supplemental oxygen [4, 5]. Remdesivir is recommended for administration within 7–10 days of symptom onset, as it provides the greatest benefit when administered early in the course of the disease [4-6].

Patients with COVID-19 and chronic kidney disease (CKD) have a higher risk of mortality than those without CKD [7]. Despite the need for treatment options for patients with severe renal insufficiency, this population has been excluded from most randomized controlled trials (RCTs) examining the efficacy of remdesivir [8-10]. This exclusion was primarily due to concerns about the potential toxicity of sulfobutylether- β -cyclodextrin (SBECD) accumulation [11]. However, the safety of remdesivir in this population has been indicated by a recent randomized controlled trial (REDPINE trial) [12] and several observational studies [13-16]. Currently, the U.S. Food and Drug Administration approves the use of remdesivir without dose adjustment in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m² [17]. However, this is an extension of the indication from a safety perspective, and the effectiveness of remdesivir for patients with COVID-19 and severe renal insufficiency remains unknown.

Thus, this study aimed to evaluate whether early initiation of remdesivir in patients with COVID-19 and severe renal insufficiency reduces the risk of mortality or invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO).

METHODS

1. Study design and setting

This retrospective cohort study utilized data from the COVID-19 Registry Japan (COVIREGI-JP), a nationwide registry of inpatients with COVID-19 in Japan [18]. As of March 2024, the COVIREGI-JP included more than 93,000 patients at 642 facilities. To assess the effectiveness of remdesivir, we emulated a hypothetical target trial. In this trial, patients with COVID and severe renal insufficiency within 7 days of symptom onset, as well as noncritical patients (defined as those requiring low-flow oxygen or no supplemental oxygen), were started on remdesivir within the first 2 days of admission. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [19].

2. Data collection

We modified the case report form of the International Severe Acute Respiratory and Emerging Infection Consortium [20] to collect study data. Data collection and management were conducted using Research Electronic Data Capture (REDCap), hosted at the Joint Center for Researchers, Associates and Clinicians (JCRAC) data center of the National Center for Global Health and Medicine.

3. Participants

We included patients who met all of the following criteria: (1) patients with a positive COVID-19 test result; (2) patients admitted to Japanese medical institutions between January 1, 2020, and May 8, 2023; and (3) patients with pre-existing severe renal insufficiency before admission (serum creatinine ≥ 3 mg/dL, on maintenance dialysis, or kidney transplant recipients). We excluded patients who met any of the following criteria: (1) aged <18 years; (2) pregnant; (3) having aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >5 times the upper limit of normal; (4) already receiving high-flow oxygen on admission, such as high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NPPV), IMV; (5) >7 days from symptom onset to admission; (6) started on remdesivir before admission; (7) missing symptom onset date.

4. Definition of treatment strategy and exposure period

Assuming the target trial, patients were classified according to whether they started remdesivir within the first 2 days after admission. In the main analysis, we defined the exposure period as the period during which the following two conditions were met simultaneously: (1) from symptom onset to the 7-day time point and (2) during the first 2 days after admission (Figure 1).

5. Definition of covariates

Eight epidemic waves had occurred in Japan by May 8, 2023. Based on previous studies, we have identified the following waves: first wave (January 16, 2020 to June 13, 2020); second wave (June 14, 2020 to October 9, 2020); third wave (October 10, 2020 to

February 28, 2021); fourth wave (March 1, 2021 to June 20, 2021), fifth wave (June 21, 2021 to December 16, 2021); sixth wave (December 17, 2021 to June 24, 2022); seventh wave (June 25, 2022 to October 15, 2022); and eighth wave (October 16, 2022 to May 8, 2023) [21, 22]. From the sixth wave, Omicron strains dominated the epidemic. Patients were considered to have a history of vaccination if they had completed at least a 2-dose primary series. Smoking status was classified into three categories: current, past, and never. Comorbidities were based on information obtained at admission. The National Early Warning Score (NEWS) [23] was used as a continuous variable for COVID-19 severity at admission. Immunocompromised status was defined as meeting one of the following criteria: neutrophil count $<500/\mu\text{L}$, asplenia, primary immunodeficiency syndrome, hematopoietic cell transplantation, solid organ transplantation, corticosteroid use (prednisolone equivalent >20 mg/day for >1 month), chemotherapy within the past 3 months, radiation therapy within the past 3 months, or non-corticosteroid immunosuppressive drug use within the past 3 months. Neutralizing antibody drug use was determined by whether patients received casirivimab/imdevimab or sotrovimab. Immunomodulator use was determined based on whether patients received tocilizumab or baricitinib.

6. Definition of the endpoint

The primary endpoint was the composite of death and IMV/ECMO. Patients were followed up from the landmark time point for up to 28 days until the first occurrence of discharge, transfer, or death. If discharged alive before 28 days, patients were right-censored at 28 days [24], and if transferred within 28 days, patients were censored at that time.

7. Statistical analysis

Baseline summary statistics of the participants were calculated. Values are reported as medians (interquartile ranges) or numbers (percentages), as appropriate.

The intention-to-treat (ITT) effect of starting remdesivir within 7 days of symptom onset was estimated. Using the landmark method, we could evaluate the prognosis from the landmark time point, addressing immortal time bias [25]. Using this approach, patients whose outcomes occurred before the landmark time point were excluded from the analysis, and patients were classified by exposure status during this period. As remdesivir initiation is recommended within 7 days of symptom onset [5], the predefined day 7 of symptom onset was used as the landmark time point for the primary analysis in this study. Patients were classified into the remdesivir group if they were admitted to the hospital at the landmark time point (day 7 of symptom onset), and remdesivir was started within the first 2 days of admission (defined as the exposure period). Unadjusted survival probability was estimated using the Kaplan–Meier method. We estimated the adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for the initiation of remdesivir on outcome occurrence using Cox proportional hazards regression. The following factors were adjusted for: sex, age, smoking status, epidemic phase (waves 1–8), vaccination history, number of days from onset to admission, physician-diagnosed obesity, hypertension, dyslipidemia, immunocompromised status, Charlson comorbidity index (CCI), maintenance dialysis before admission, NEWS at admission, absolute lymphocyte count, ALT, lactate dehydrogenase (LDH), C-reactive protein (CRP), and use of anticoagulants before admission. To avoid over-adjustment owing to intermediate factors, we adjusted for the following combination therapies for COVID-19 if initiated before the end of the exposure period: neutralizing antibodies, immunomodulators, corticosteroids, and molnupiravir. Log-log survival curves were used to assess the proportional hazards assumption. A cluster-robust standard error was used to address clustering effects across hospitals.

7.1. Sensitivity analysis

Sensitivity analyses were performed to evaluate the robustness of the results: (1) The landmark time points were set at days 5 and 10 of symptom onset. (2) In Japan, remdesivir was approved late in the first wave of the epidemic (May 7, 2020); therefore, we excluded the first wave because it was highly unlikely that all patients equally had the opportunity to receive remdesivir in the first wave. (3) To account for the possibility of different baseline hazards at different hospitals, we included hospitals as a random effect in the analysis.

7.2. Subgroup analysis

The effects of remdesivir were evaluated using similar methods to those used in the primary analysis, in subgroups that might have differed in the effectiveness of remdesivir. The subgroups were (1) maintenance dialysis prior to admission, (2) respiratory failure on admission, (3) before or after the Omicron variant epidemic, (4) time between onset to admission (≤ 4 days vs. > 4 days), and (5) vaccination status. Additionally, we included interaction terms, subgroup variables, remdesivir use, and confounders in the outcome model to test for interactions. The statistical significance of the interaction test was set at two-sided $p < 0.05$. This interaction analysis was exploratory in purpose; therefore, we did not correct for p-values.

7.3. Missing data

Missing data included vaccination history and smoking status in preadmission data, and NEWS and blood test at admission data. A multiple imputation method with chained

equations was used to generate 50 datasets and the estimates obtained for each dataset were integrated using Rubin's rule [26].

All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

8. Ethical issues

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kyoto University (approval number: R4149-1). The requirement for written patient consent was waived owing to the retrospective nature of this study. Information regarding opting out of the study is available on the study website.

RESULTS

1. Patient characteristics

Out of 2,136 initially considered patients, 396 were excluded, leaving 1,740 candidates for landmark analysis (Figure 2). By day 7 of symptom onset, 291 patients were excluded due to outcomes (56 deaths, 74 IMV/ECMO initiations, 81 discharges, and 80 transfers). Thus, finally, 1,449 patients were included in the landmark analysis: 272 were assigned to the remdesivir group, while the remaining 1,177 were classified as controls, with 84 of them receiving remdesivir after the exposure period. Table 1 presents the characteristics of the landmark cohort. The median age was 74 years (interquartile range [IQR], 62–84), 992 (68.5%) participants were male, and 98.7% were Japanese. Compared with the control group,

the remdesivir group had more patients in the sixth or later waves of the epidemic (79.4% vs. 54.5%), a higher vaccination rate (65.0% vs. 43.9%), a higher proportion of respiratory failure at admission (41.2% vs. 21.5%), a higher proportion of immunocompromised status (15.0% vs. 7.7%) (details are provided in Supplementary Table 1), and a higher proportion of corticosteroid use as combination therapy for COVID-19 (34.2% vs. 13.8%). Remdesivir was administered for a median duration of 5 days (IQR, 3-5): 137 (50.4%) patients received treatment for 5 days; 77 (28.3%), 3 days; and 25 (9.2%), 10 days (Supplementary Figure 1). Additionally, 249 (91.5%) patients received 200 mg on day one and 100 mg/day thereafter.

The following covariates had missing values in the remdesivir and control groups: ALT, 6.1% (1.8% vs. 7.1%); LDH, 8.8% (7.0% vs. 9.2%); lymphocyte count, 11.5% (7.7% vs. 12.4%); NEWS, 19.9% (11.4% vs. 21.8%); CRP, 7.2% (2.2% vs. 8.3%); smoking status, 16.0% (14.7% vs. 16.3%); and vaccination status, 16.3% (18.0% vs. 15.9%).

2. Endpoint

During the 28 days from the landmark timepoint, 19 (7.0%) and 136 (11.6%) patients in the remdesivir and control groups, respectively, had an outcome. Thirty-four (12.5%) and 145 (12.3%) patients in the remdesivir and control groups, respectively, were censored due to hospital transfer during the follow-up period (Table 2). Figure 3 shows the Kaplan–Meier survival curves for the two groups.

Figure 4 illustrates the results of primary, sensitivity, and subgroup analyses. In the primary analysis, the remdesivir group had a lower risk of mortality or IMV/ECMO initiation than the control group (HR, 0.44; 95% CI, 0.23–0.83). This finding was consistent across the four sensitivity analyses. The association between remdesivir use and outcome was similar across subgroups: p for interaction for maintenance dialysis before admission was 0.22;

respiratory failure on admission, 0.68; before or after the Omicron variant epidemic, 0.13; time between onset to admission (≤ 4 days vs. $4 > \text{days}$), 0.33; and vaccination status, 0.48.

DISCUSSION

Among 1,449 noncritical patients with COVID-19 and severe renal insufficiency admitted to Japanese hospitals within 7 days of symptom onset, initiation of remdesivir within the first 2 days of admission was associated with a lower risk of mortality or IMV/ECMO initiation compared with non-initiation.

Few RCTs have investigated the efficacy of remdesivir in patients with COVID-19 and renal insufficiency. In the REDPINE trial, remdesivir plus standard therapy did not reduce all-cause mortality or invasive mechanical ventilation compared with standard therapy alone among patients with oxygen saturation $\leq 94\%$ on room air or requiring oxygen supplementation and with an eGFR $< 30 \text{ mL/min/1.73 m}^2$ due to CKD or AKI [12]. However, this trial was terminated prematurely due to recruitment issues after the randomization of 249 patients. Thus, the study was underpowered to detect the efficacy of remdesivir [12]. The Phase III CATCO trial, a Canadian sub-study of the WHO's SOLIDARITY, included 59 patients hospitalized with COVID-19 (remdesivir, 34; standard therapy, 25) with a baseline eGFR $< 30 \text{ mL/min/1.73 m}^2$ [27]. Although no significant differences were observed in the initiation of invasive mechanical ventilation or mortality, interpretation of the results is constrained by the small sample size [27]. The present study successfully evaluated the effectiveness of remdesivir in a large cohort comprising 1,449 participants.

An observational study examined 1,010 patients undergoing dialysis who had COVID-19 and were enrolled by June 19, 2021 [28]. After propensity score matching, 392 patients were included in the analysis, and remdesivir treatment was associated with a

decreased risk of mortality (HR, 0.45; 95% CI, 0.26–0.80). However, immortal time bias was a concern in the study. The use of landmark analysis in our study confirmed the effectiveness of remdesivir, even after accounting for immortal time bias.

No statistically significant differences were observed in the effectiveness of remdesivir among the subgroups examined in the present study. However, the effectiveness of remdesivir may be different between patients with and without maintenance dialysis. Patients with maintenance dialysis often experience immune deficiency due to lymphocyte dysfunction and abnormal cytokine levels [29], which could have contributed to the increased benefit of remdesivir. Other potential reasons for the heterogeneity are as follows: (1) Heterogeneity of remdesivir exposure intensity—the effectiveness of remdesivir may be lower in non-dialysis patients if it is discontinued early or if the period between symptom onset and the initiation of remdesivir treatment is long. However, this was unlikely in the present study because no apparent difference was observed in the distribution of the duration of remdesivir administration (Supplementary Figure 2) or days from onset to remdesivir administration (median [IQR] days for dialysis and non-dialysis, 2 [1–5] vs. 2 [1–4], respectively). (2) Heterogeneity due to confounding factors—the quality of care at the hospital can be a confounding factor that distorts the effectiveness of remdesivir. Hospitals specializing in COVID-19 care may be associated with both remdesivir use and lower COVID-19 mortality. This association could have introduced a bias, resulting in the overestimation of the effectiveness of remdesivir. If patients with maintenance dialysis are more likely to be admitted in such hospitals than non-dialysis patients, confounding may create a heterogeneity that remdesivir is associated with better outcomes in patients with maintenance dialysis. This possibility cannot be dismissed, as this study solely identified hospitals by ID numbers, lacking detailed information to adjust for the quality of care in each hospital. (3) Heterogeneity due to random variations—heterogeneity due to chance may have occurred because the stratification

reduced the sample size for each group. Further research is required to determine the possible heterogeneity of remdesivir effectiveness.

No significant differences were observed in the effectiveness of remdesivir between the outbreak periods of Omicron and non-Omicron strains. This aligns with previous findings indicating similar efficacy of remdesivir in vitro against the Omicron variant and earlier strains [30], as well as results from a retrospective study utilizing large datasets from routine clinical practice [31].

Limitations

The strength of this study lies in its contribution to reducing the knowledge gap in the treatment of patients with COVID-19 and severe renal insufficiency. However, the present study had several limitations. First, owing to substantial missing data regarding vaccination dates, vaccination status was classified solely based on the number of vaccinations. Consequently, patients vaccinated within 14 days of the second vaccination were classified as vaccinated. Second, data on do-not-resuscitate (DNR) orders were unavailable. Patients with DNR instructions upon admission may have been excluded from receiving remdesivir during periods of inadequate remdesivir supply, particularly during the early stages of the pandemic. Third, information regarding underlying diseases causing baseline renal dysfunction was unavailable. Additionally, information regarding the duration of dialysis was unavailable for patients with maintenance dialysis. Fourth, COVIREGI-JP is a registry reliant on voluntary participation of hospitals and may not be representative of all patients with COVID-19 in Japan [32]. Additionally, this registry focuses on hospitalized patients, which introduces a selection bias by excluding those treated on an outpatient basis. Outpatients may be less likely to benefit from remdesivir due to their lower risk of serious outcomes, such as death or ventilator

initiation. Although subgroup analyses based on severity at admission (i.e., with or without respiratory failure) showed no significant differences in the effectiveness of remdesivir, caution should be warranted when generalizing these findings to non-hospitalized patients. Fifth, 98.7% of the patients with available race information were Japanese. However, no clear differences in the efficacy of remdesivir by race have been reported previously; therefore, the transportability of the results to non-Japanese individuals is deemed acceptable.

CONCLUSIONS

For noncritical patients with COVID-19 and severe renal insufficiency at admission, the initiation of remdesivir early after disease onset, within the first 2 days of admission, led to a lower risk of mortality or IMV/ECMO initiation, than non-initiation of remdesivir.

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346 **Data availability.** Data on an individual level is shared with limitation to participating
347 healthcare facilities through applications to COVIREGI-JP.

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REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available at <https://data.who.int/dashboards/covid19/deaths?n=c> (accessed 18 March 2024).
2. Smits PD, Gratzl S, Simonov M, *et al.* Risk of COVID-19 breakthrough infection and hospitalization in individuals with comorbidities. *Vaccine*, **2023**; 41: 2447-2455. doi: 10.1016/j.vaccine.2023.02.038.
3. Amstutz A, Speich B, Mentré F, *et al.* Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Respir Med*, **2023**; 11: 453-464. doi: 10.1016/S2213-2600(22)00528-8.
4. National Institutes of Health COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National institutes of health. Available at <https://www.covid19treatmentguidelines.nih.gov/> (accessed 18 March 2024).
5. Bhimraj A, Morgan RL, Shumaker AH, *et al.* Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Infectious Diseases Society of America* 2023; version 11.0.0. Available at <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/> (accessed 18 March 2024).
6. Godwin PO, Polsonetti B, Caron MF, Oppelt TF. Remdesivir for the treatment of COVID-19: a narrative review. *Infect Dis Ther*, **2024**; 13: 1-19. doi: 10.1007/s40121-023-00900-3.
7. Flythe JE, Assimon MM, Tugman MJ, *et al.* Characteristics and outcomes of individuals with pre-existing kidney disease and COVID-19 admitted to intensive care units in the United States. *Am J Kidney Dis*, **2021**; 77: 190-203.e1. doi: 10.1053/j.ajkd.2020.09.003.

8. Beigel JH, Tomashek KM, Dodd LE, *et al.* Remdesivir for the treatment of Covid-19—final report. *N Engl J Med*, **2020**; 383: 1813-1826. doi: 10.1056/NEJMoa2007764.
9. Pan H, Peto R, Henao Restrepo AM, *et al.* Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*, **2022**; 399: 1941-1953. doi: 10.1016/S0140-6736(22)00519-0.
10. Gottlieb RL, Vaca CE, Paredes R, *et al.* Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med*, **2022**; 386: 305-315. doi: 10.1056/NEJMoa2116846.
11. Adamsick ML, Gandhi RG, Bidell MR, *et al.* Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*, **2020**; 31: 1384-1386. doi: 10.1681/ASN.2020050589.
12. Santos JR, Goldman JD, Tuttle KR, *et al.* The REDPINE study: efficacy and safety of remdesivir in people with moderately and severely reduced kidney function hospitalized for COVID-19 pneumonia; 2023; Copenhagen, Denmark. Available at Poster presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 15–18, https://www.askgileadmedical.com/docs/conference/JoseRamon_ECCMID2023_Redpine_P2635@pdf (accessed 30 April 2024).
13. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. *Antimicrob Agents Chemother*, **2021**; 65: e02290-20. doi: 10.1128/AAC.02290-20.

14. Estiverne C, Strohbehn IA, Mithani Z, *et al.* Remdesivir in patients with estimated GFR <30 ml/min per 1.73 m² or on renal replacement therapy. *Kidney Int Rep*, **2021**; 6: 835-838. doi: 10.1016/j.ekir.2020.11.025.
15. Sunny S, Samaroo-Campbell J, Abdallah M, Luka A, Quale J. Is remdesivir safe in patients with renal impairment? Experience at a large tertiary urban medical center. *Infection*, **2023**; 51: 247-252. doi: 10.1007/s15010-022-01850-7.
16. Yang E, Choi HZ, Kim S, *et al.* Propensity score matched analysis for the safety and effectiveness of remdesivir in COVID-19 patients with renal impairment. *BMC Infect Dis*, **2024**; 24: 3. doi: 10.1186/s12879-023-08859-9.
17. Gilead Sciences Inc. VEKLURY-remdesivir injection, powder, lyophilized, for solution: US prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214787s019lbl.pdf (accessed 18 March 2024).
18. National Center for Global Health and Medicine. COVID-19 registry Japan. Available at <https://Rebind.ncgm.go.jp/coviregi/> (accessed 18 March 2024).
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*, **2007**; 147: 573-577. doi: 10.7326/0003-4819-147-8-200710160-00010.
20. International Severe Acute Respiratory and emerging Infection Consortium (ISARIC). COVID-19 clinical research resources. Available at <https://Isaric.org/research/covid-19-clinical-research-resources/covid-19-crf/> (accessed 18 March 2024).

21. Lee H, Chubachi S, Namkoong H, *et al.* Characteristics of hospitalized patients with COVID-19 during the first to fifth waves of infection: a report from the Japan COVID-19 Task Force. *BMC Infect Dis*, **2022**; 22: 935. doi: 10.1186/s12879-022-07927-w.
22. Tanaka H, Chubachi S, Asakura T, *et al.* Characteristics and clinical effectiveness of COVID-19 vaccination in hospitalized patients in Omicron-dominated epidemic wave—a nationwide study in Japan. *Int J Infect Dis*, **2023**; 132: 84-88. doi: 10.1016/j.ijid.2023.04.399.
23. The National Health Service England. National early warning score (NEWS). Available at <https://www.england.nhs.uk/ourwork/clinical-policy/sepsis/nationalearlywarningscore/> (accessed 24 March 2024).
24. Burnim MS, Wang K, Checkley W, Nolley EP, Xu Y, Garibaldi BT. The effectiveness of high-flow nasal cannula in coronavirus disease 2019 pneumonia: a retrospective cohort study. *Crit Care Med*, **2022**; 50: e253-e262. doi: 10.1097/CCM.0000000000005309.
25. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol*, **1983**; 1: 710-719. doi: 10.1200/JCO.1983.1.11.710.
26. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley & Sons, 2004.
27. Cheng M, Fowler R, Murthy S, Pinto R, Sheehan NL, Tseng A. Remdesivir in patients with severe kidney dysfunction: a secondary analysis of the CATCO randomized trial. *JAMA Netw Open*, **2022**; 5: e2229236. doi: 10.1001/jamanetworkopen.2022.29236.
28. Kikuchi K, Nangaku M, Ryuzaki M, *et al.* Survival and predictive factors in dialysis patients with COVID-19 in Japan: a nationwide cohort study. *Ren Replace Ther*, **2021**; 7: 59. doi: 10.1186/s41100-021-00378-0.

29. Zeng B, Zhou J, Peng D, *et al.* The prevention and treatment of COVID-19 in patients treated with hemodialysis. *Eur J Med Res*, **2023**; 28: 410-419. doi: 10.1186/s40001-023-01389-9.
30. Takashita E, Kinoshita N, Yamayoshi S, *et al.* Efficacy of antibodies and antiviral drugs against Covid-19 Omicron variant. *N Engl J Med*, **2022**; 386: 995-998. doi: 10.1056/NEJMc2119407.
31. Mozaffari E, Chandak A, Gottlieb RL, *et al.* Remdesivir reduced mortality in immunocompromised patients hospitalized for COVID-19 across variant waves: findings from routine clinical practice. *Clin Infect Dis*, **2023**; 77: 1626-1634. doi: 10.1093/cid/ciad460.
32. Hayakawa K, Asai Y, Matsunaga N, *et al.* Evaluation of the representativeness of data in the COVID-19 Registry Japan during the first six waves of the epidemic. *Glob Health Med*, **2022**; 4: 204-209. doi: 10.35772/ghm.2022.01033.

Table 1. Baseline characteristics of patients in the landmark cohort

	Remdesivir group (Remdesivir in the exposure period) (n=272)	Control group (No remdesivir in the exposure period) (n=1177)	Total (n=1449)
Age (years)	74.5 (60.5–84)	74 (62–84)	74 (62–84)
Male	195 (71.7%)	797 (67.7%)	992 (68.5%)
BMI (kg/m ²) [†]	22.1 (19.9–26.0)	22.1 (19.8–25.0)	22.1 (19.8–25.2)
Japanese [†]	252 (99.2%)	1083 (98.6%)	1335 (98.7%)
Endemic wave			
First wave	0 (0.0%)	40 (3.4%)	40 (2.8%)
Second wave	3 (1.1%)	65 (5.5%)	68 (4.7%)
Third wave	18 (6.6%)	288 (24.5%)	306 (21.1%)
Fourth wave	13 (4.8%)	83 (7.1%)	96 (6.6%)
Fifth wave	22 (8.1%)	59 (5.0%)	81 (5.6%)
Sixth wave	83 (30.5%)	281 (23.9%)	364 (25.1%)
Seventh wave	81 (29.8%)	199 (16.9%)	280 (19.3%)
Eighth wave	52 (19.1%)	162 (13.8%)	214 (14.8%)
Vaccination (%) [†]	145 (65.0%)	435 (43.9%)	580 (47.8%)
Smoking status [†]			
Never smoked	105 (45.3%)	497 (50.5%)	602 (49.5%)
Current smoker	25 (10.8%)	122 (12.4%)	147 (12.1%)
Former smoker	102 (44.0%)	366 (37.2%)	468 (38.5%)

History of COVID-19 [†]	4 (1.5%)	17 (1.5%)	21 (1.5%)
Obesity	23 (8.5%)	69 (5.9%)	92 (6.3%)
Cardiovascular disease	77 (28.3%)	374 (31.8%)	451 (31.1%)
Cerebrovascular disease	53 (19.5%)	202 (17.2%)	255 (17.6%)
Dementia	36 (13.2%)	137 (11.6%)	173 (11.9%)
Respiratory disease	33 (12.1%)	111 (9.4%)	144 (9.9%)
Rheumatologic disease	6 (2.2%)	35 (3.0%)	41 (2.8%)
Peptic ulcer disease	4 (1.5%)	31 (2.6%)	35 (2.4%)
Liver disease	12 (4.4%)	63 (5.4%)	75 (5.2%)
Diabetes	113 (41.5%)	511 (43.4%)	624 (43.1%)
Hemiplegia	11 (4.0%)	43 (3.7%)	54 (3.7%)
Malignancy	39 (14.3%)	148 (12.6%)	187 (12.9%)
Hemodialysis	101 (37.1%)	507 (43.1%)	608 (42.0%)
Kidney transplant recipients	8 (2.9%)	32 (2.7%)	40 (2.8%)
HIV	0 (0.0%)	1 (0.1%)	1 (0.1%)
Hypertension	172 (63.2%)	726 (61.7%)	898 (62.0%)
Dyslipidemia	73 (26.8%)	266 (22.6%)	339 (23.4%)
Immunocompromised [†]	38 (15.0%)	87 (7.7%)	125 (9.1%)
Charlson comorbidity index	4 (3–5)	4 (3–5)	4 (3–5)
Respiratory failure at admission	112 (41.2%)	253 (21.5%)	365 (25.2%)
NEWS [†]	3 (1–5)	2 (0–4)	2 (1–4)

AST (IU/L) [†]	24 (16–36)	21 (15–30)	22 (15–31)
ALT (IU/L) [†]	14 (10–22)	13 (9–19)	13 (9–20)
LDH (IU/L) [†]	250 (202–325)	223 (186–280)	227 (188–289)
CRP (mg/dL) [†]	3.58 (1.35–8.48)	2.44 (0.69–6.87)	2.61 (0.83–7.14)
Lymphocyte count ($\times 10^3/\mu\text{L}$) [†]	0.78 (0.53–1.20)	0.81 (0.56–1.18)	0.80 (0.55–1.18)
Use of anticoagulation before admission	36 (13.2%)	144 (12.2%)	180 (12.4%)
Combination therapy*			
Tocilizumab	8 (2.9%)	7 (0.6%)	15 (1.0%)
Baricitinib	4 (1.5%)	0 (0.0%)	4 (0.3%)
Casirivimab/imdevimab	11 (4.0%)	24 (2.0%)	35 (2.4%)
Sotrovimab	20 (7.4%)	180 (15.3%)	200 (13.8%)
Molnupiravir	10 (3.7%)	200 (17.0%)	210 (14.5%)
Nirmatrelvir/ritonavir	0 (0.0%)	6 (0.5%)	6 (0.4%)
Corticosteroid	93 (34.2%)	162 (13.8%)	255 (17.6%)
Days from onset to admission	1 (0–3)	1 (0–3)	1 (0–3)
Days from onset to remdesivir administration	1 (1–3)	NA	NA
Duration of remdesivir administration	5 (3–5)	NA	NA

BMI, body mass index; HIV, human immunodeficiency virus; NEWS, National Early Warning

Score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate

dehydrogenase; CRP, C-reactive protein.

† Percentages were calculated with missing data removed from the denominator. The number of missing data for the remdesivir group, control group, and total are as follows: BMI: 32, 168, 200; Japanese: 18, 79, 97; vaccination: 49, 187, 236; smoking status: 40, 192, 232; history of COVID-19: 2, 10, 12; immunocompromised: 19, 53, 72; NEWS: 31, 257, 288; AST: 5, 82, 87; ALT: 5, 84, 89; LDH: 19, 108, 127; CRP: 6, 98, 104; lymphocyte count: 21, 146, 167.

* Combination therapies for COVID-19 if initiated before the end of the exposure period.

Table 2. Comparison of 28-day outcome from 7-day landmark time point between the remdesivir and control groups

	Remdesivir group (Remdesivir in the exposure period) (n=272)	Control group (No remdesivir in the exposure period) (n=1177)
Transfer	34 (12.5%)	145 (12.3%)
Discharge	194 (71.3%)	764 (64.9%)
Hospitalized without outcome	25 (9.2%)	132 (11.2%)
Death or IMV/ECMO	19 (7.0%)	136 (11.6%)
Death	16 (5.9%)	109 (9.3%)
IMV/ECMO	3 (1.1%)	27 (2.3%)

IMV/ECMO, invasive mechanical ventilation or extracorporeal membrane oxygenation

FIGURE LEGENDS

Figure 1. Study design

The exposure period was defined as the period during which the following two conditions were met simultaneously: (1) from symptom onset to the 7-day time point and (2) during the first 2 days after admission.

Figure 2. Flow chart of study participants

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HFNC, high-flow nasal cannula; NPPV, noninvasive positive pressure ventilation; IMV/ECMO, invasive mechanical ventilation or extracorporeal membrane oxygenation

Figure 3. Kaplan–Meier survival curves for the remdesivir and control groups

Kaplan–Meier survival probabilities for outcome-free survival by treatment group after the landmark time point. The primary endpoint was a composite of death and initiation of invasive mechanical ventilation or extracorporeal membrane oxygenation. The black and gray lines indicate the remdesivir and control groups, respectively.

Figure 4. Primary, sensitivity and subgroup analyses assessing the 28-day outcome in the remdesivir and control groups

HR, hazard ratio; HD, hemodialysis; ALT, alanine aminotransferase; NEWS, The National Early Warning Score; LDH, lactate dehydrogenase; CRP, C-reactive protein.

*Estimated from landmark analysis adjusted for sex, age, smoking status, epidemic wave,

vaccination status, days from symptom onset to admission, obesity, hypertension, dyslipidemia, immunocompromised status, hemodialysis, Charlson comorbidity index, NEWS on admission, ALT on admission, LDH on admission, CRP on admission, lymphocyte count on admission, anticoagulation before admission, combination therapies for COVID-19 if initiated before the end of the exposure period: neutralizing antibody (casirivimab/imdevimab or sotrovimab), immunomodulator (tocilizumab or baricitinib), corticosteroids, and molnupiravir. To account for missing data, multiple imputation methods with chained equations were used to generate 50 datasets, and the estimates obtained for each dataset were integrated using Rubin's rule.

Figure 1

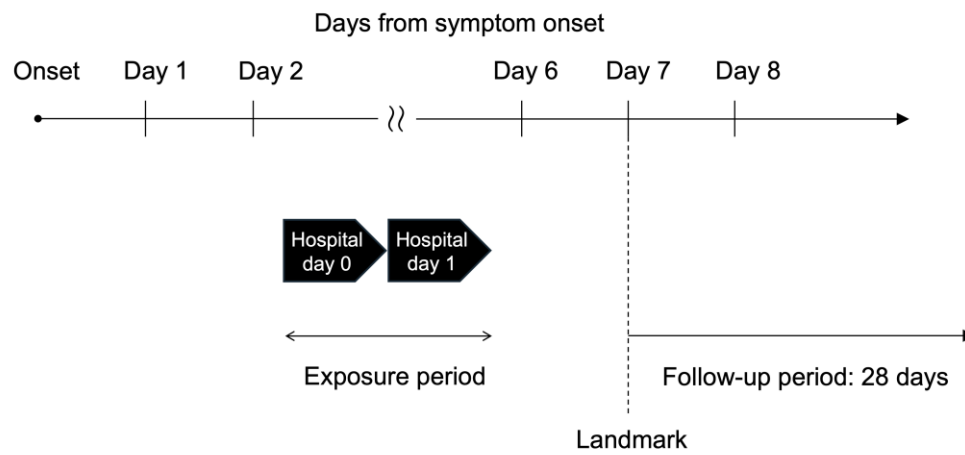


Figure 2

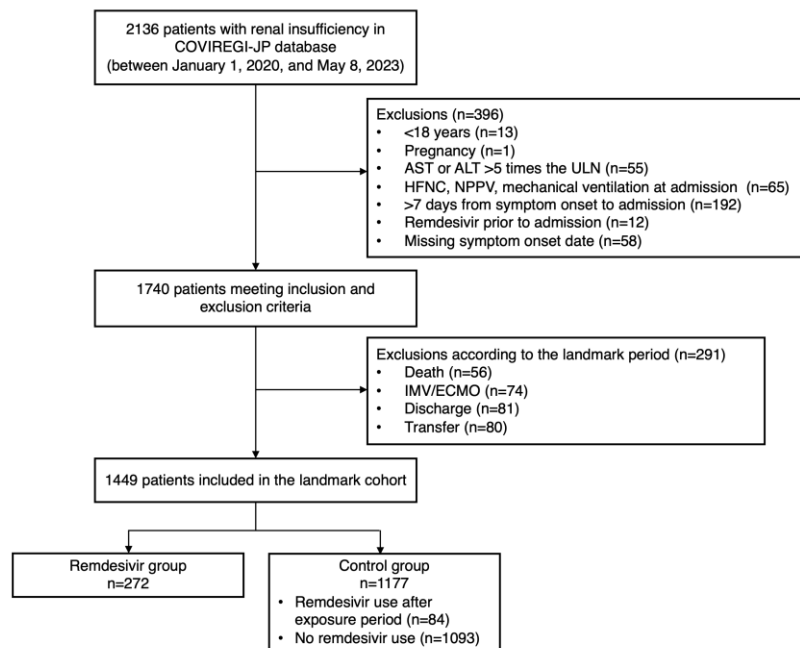


Figure 3

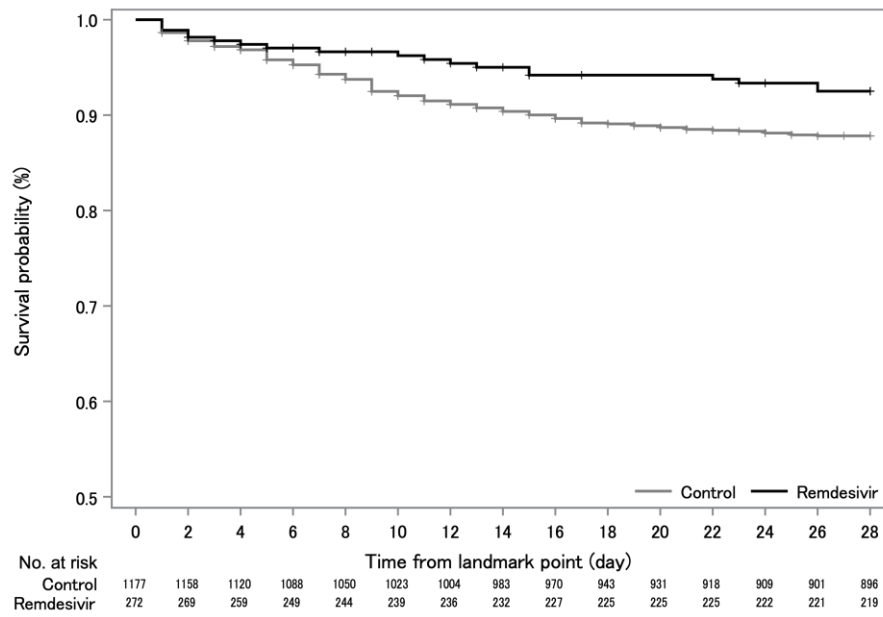
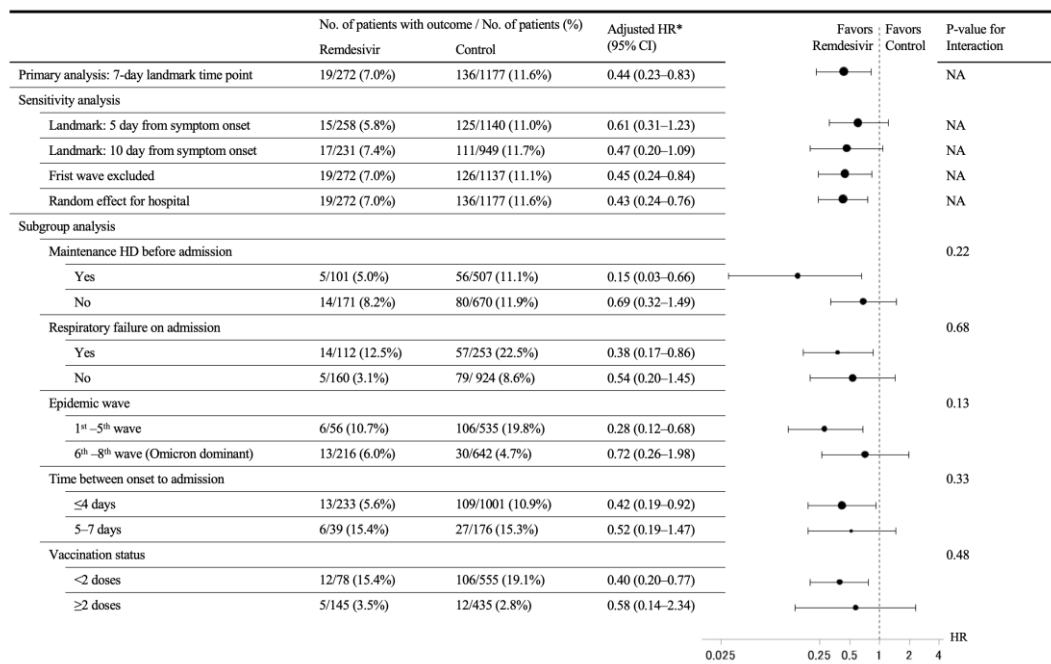


Figure 4



ACKNOWLEDGEMENT

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[https://www.tandfonline.com/\[https://doi.org/10.1080/23744235.2024.2409729\]](https://www.tandfonline.com/[https://doi.org/10.1080/23744235.2024.2409729]).

SUPPLEMENTARY MATERIAL

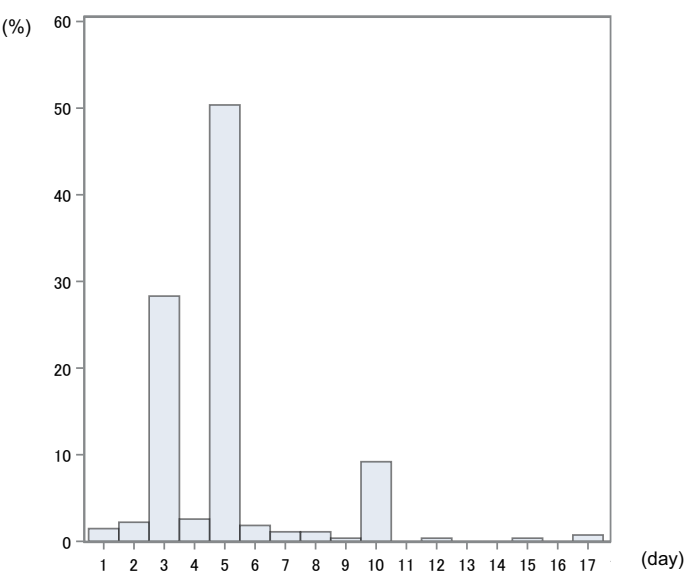
Supplementary Table 1. Details of immunocompromised status.

	Remdesivir group (n=272)	Control group (n=1177)	Total (n=1449)
Neutrophil Count <500/ μ L	2 (0.8%)	0 (0.0%)	2 (0.1%)
Asplenia	1 (0.4%)	0 (0.0%)	1 (0.1%)
Primary Immunodeficiency Syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematopoietic Cell Transplantation	0 (0.0%)	1 (0.1%)	1 (0.1%)
Solid Organ Transplantation	12 (4.7%)	34 (3.0%)	46 (3.3%)
Corticosteroid Use	5 (2.0%)	25 (2.2%)	30 (2.2%)
Chemotherapy	8 (3.2%)	19 (1.7%)	27 (2.0%)
Radiation Therapy	0 (0.0%)	1 (0.1%)	1 (0.1%)
Non-Corticosteroid Immunosuppressive Drug Use	19 (7.5%)	54 (4.8%)	73 (5.3%)

Multiple conditions may apply in some patients.

Percentages were calculated with missing data removed from the denominator. The number of missing data for the remdesivir group, control group, and total are as follows:
immunocompromised: 19, 53, 72.

Supplementary Figure 1. Duration of remdesivir use in the remdesivir group.



Supplementary Figure 2. Duration of remdesivir use in the dialysis and non-dialysis groups.

