

Impact of Remdesivir on SARS-CoV-2 Clearance in a Real-Life Setting: A Matched-Cohort Study

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Background: Evidence regarding the impact of remdesivir (RDV) on SARS-CoV-2 viral clearance (VC) is scarce. The aim of this study was to compare VC timing in hospitalized COVID-19 patients who did or did not receive RDV.

Methods: This was a matched-cohort study of patients hospitalized with pneumonia, a SARS-CoV-2-positive nasopharyngeal swab (NPS) at admission, and at least one NPS during follow-up. Patients who received RDV (cases) and those who did not (controls) were matched in a 1:2 ratio by age, sex, and PaO₂/FiO₂ (P/F) values at admission. NPSs were analyzed using real-time polymerase chain reaction. Time to VC (within 30 days after hospital discharge) was estimated using the Kaplan–Meier curve. A multivariable Cox proportional hazard model was fitted to determine factors associated with VC.

Results: There were 648 patients enrolled in the study (216 cases and 432 controls). VC was observed in 490 patients (75.6%), with a median time of 25 (IQR 16–34) days. Overall, time to VC was similar between cases and controls ($p = 0.519$). However, time to VC was different when considering both RDV treatment status and age ($p = 0.007$). A significant finding was also observed when considering both RDV treatment status and P/F values at admission ($p = 0.007$). A multivariate analysis showed that VC was associated with a younger age (aHR = 0.990, 95% CI 0.983–0.998 per every 10-year increase in age; $p = 0.009$) and a higher baseline P/F ratio (aHR=1.275, 95% CI 1.029–1.579; $p=0.026$), but not with RDV treatment status.

Conclusion: Time to VC was similar in cases and controls. However, there was a benefit associated with using RDV in regard to time to VC in younger patients and in those with a P/F ratio ≤ 200 mmHg at hospital admission.

Keywords: COVID-19, remdesivir, SARS-CoV-2, viral clearance

Introduction

Remdesivir (RDV) is a nucleotide prodrug of an adenosine analog. It binds to RNA-dependent RNA polymerase and inhibits viral replication by prematurely terminating RNA transcription.¹ RDV is active in vitro against a broad spectrum of different viruses including Ebola, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome-related coronavirus (MERS-CoV), and SARS-CoV-2.^{2–4} In particular, different preclinical studies have demonstrated the efficacy of RDV in blocking SARS-CoV-2 infection in human cells and animal models.^{3,5,6}

Currently, RDV is the only antiviral drug approved by both the European Medicines Agency and the Food and Drug Administration for the treatment of hospitalized coronavirus disease-19 (COVID-19) patients.^{7,8} However, the efficacy of RDV as a therapeutic agent for severe COVID-19 is still in question;⁹ although, the early use of RDV in non-hospitalized

patients at high-risk of disease progression has been associated with a significantly lower risk of hospitalization or death.¹⁰ In hospitalized patients, the first stage of the Adaptive COVID-19 Treatment Trial (ACCT-1)¹¹ indicated that the use of RDV was associated with a reduced time to recovery, a reduced risk of clinical progression, and improved mortality in patients on low-flow oxygen. Other studies have also provided evidence relative to the efficacy and safety of RDV for the treatment of COVID-19.^{12–17}

In contrast, the SOLIDARITY and DisCoVeRy trials^{18,19} did not find a significant effect of RDV on overall mortality, the initiation of ventilation, or hospital-stay duration. It is on this basis that the World Health Organization does not recommend the use of RDV in COVID-19 hospitalized patients.²⁰ In addition, evidence for the effect of RDV on SARS-CoV-2 viral clearance (VC) is scarce and contradictory. Different studies^{19,21,22} have shown that the use of RDV is not associated with nasopharyngeal viral load changes, while other studies^{23,24} have demonstrated that RDV treatment was associated with faster viral decay. However, these studies were all characterized by small sample sizes or follow-up periods that did not exceed the hospitalization period. Therefore, this large-sample-size study was conducted to evaluate the effect of RDV on VC timing in COVID-19 hospitalized patients for 1 month following hospital discharge.

Methods

This retrospective, matched-cohort study was conducted at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele (Milan, Italy). San Raffaele Hospital is a tertiary health care center designated as a COVID-19 hub by the Italian health authorities.

Adult patients (≥ 18 years) with the following characteristics were included in the study: laboratory-confirmed SARS-CoV-2 infection determined by real-time polymerase chain reaction (RT-PCR) on nasopharyngeal swab specimens performed at hospital admission; imaging studies demonstrating the presence of pneumonia (interstitial involvement and/or consolidation seen on chest x-rays or computed tomography scans); hospitalization at San Raffaele Hospital during the timeframe from February 25, 2020 to April 12, 2021; availability of at least one follow-up nasopharyngeal swab (from 5 days after hospitalization to 30 days after discharge). Patients discharged from the hospital with a positive nasopharyngeal swab continued to be followed in our center. The first follow-up nasopharyngeal swab was performed 10–14 days after hospital discharge, and if positive, was repeated every 7–10 days until negative.

Patients who received RDV were cases, while those who did not receive RDV were controls. Cases and controls were matched in a 1:2 ratio according to: age (± 5 years), sex, and the arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) value (± 10 mmHg) on admission. The $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio represents the ratio between PaO_2 as determined by arterial blood gas analysis, and the percentage of oxygen supplied (FiO_2).

Matching with replacement was used, hence, matches between cases and controls were made regardless of whether the chosen control was already paired with another case. Replacement allows the same patient to be matched more than once, ensuring the best match for each case with control patients and reducing the probability of inappropriate matches.

RDV (Gilead Sciences; GS-5734) was administered intravenously with a loading dose on the first day (200 mg) followed by 100 mg every day for 4 days. Patients treated with a 10-day course of RDV were not included in this analysis. Use of RDV was contraindicated in patients with an estimated glomerular filtration rate < 30 mL/min.

Nasopharyngeal swabs collected from patients were submitted to the San Raffaele Scientific Institute Laboratory of Microbiology, Virology and Serology for RT-PCR testing. The laboratory uses the COBAS 6800 system (Roche Diagnostics, Basel, Switzerland). COBAS 6800 amplifies the ORF1a-1b and E genes and has a limit of 100 copies of viral RNA per milliliter of transport media when amplifying gene R and 43 copies/mL when amplifying gene E. The instrument can yield qualitative (positive and negative) and quantitative results. The quantitative results are expressed in cycle threshold (Ct) values. Any Ct value below 40 corresponded to a positive nasopharyngeal swab and values above 40 were considered a negative swab.

This study was a sub-study of the COVID-19 Patients Characterization, Biobank, Treatment Response and Outcome Predictor (COVID-BioB) Study that was approved by the Ethics Committee of San Raffaele Hospital (protocol No. 34/int/2020) and registered on ClinicalTrials.gov (NCT04318366). All patients signed an informed consent form. Our research complied with the Declaration of Helsinki.

Statistical Analyses

Results are reported as medians (interquartile range, IQR) and frequencies (%). The distribution of continuous variables were compared between cases and controls using the Wilcoxon rank-sum test or the chi-square/Fisher's exact test for categorical variables.

Time to VC by nasopharyngeal swab was estimated using the Kaplan–Meier curve. The curve was then compared with the Log rank test according to some baseline characteristics. Follow-up began at hospital admission (baseline) and ended on the date of the first negative nasopharyngeal swab (within 30 days after discharge), or, in case of no negative swab, at the date of last positive swab or death. There were no competing events.

To account for indication bias associated with RDV treatment, we estimated individual propensities for receipt of RDV treatment (a propensity-score) with the use of a multivariable logistic regression model that included the following independent variables: age, gender, weight, number of comorbidities, PaO₂/FiO₂, duration of symptoms at hospital admission, concomitant use of biological drugs, concomitant use of steroids, creatinine, alanine aminotransferase, C-reactive protein, and absolute lymphocyte count at hospitalization ($>$ or $\leq 1 \times 10^9$ cells/mm³).

A multivariable Cox proportional hazard model was fitted to determine factors associated with the risk of a negative nasopharyngeal swab. The adjusted hazard ratios (aHRs) with their corresponding 95% confidence intervals (CIs) are reported. The predicted probabilities of RDV treatment (propensity-score) from the logistic regression model were used to calculate the stabilized inverse probability-weighted (IPW) weight. The multivariable Cox model included a priori factors known to have a potential effect on the outcome or on baseline covariates with a p-value < 0.05 in the univariable analysis and were analyzed using a stabilized IPW weight. These covariates were fitted as time-fixed and measured at baseline.

The model was stratified according to the time of hospital admission (before and after September 1, 2020). This was done as both RDV cases and controls were distributed differently within the two time periods and to better account for differences in the use of other concomitant treatments (mainly steroids or biological drugs) during the two time periods. The aHRs of negative nasopharyngeal swabs are reported with their corresponding 95% CIs for significant covariates. The assumption of the proportional hazard was examined by use of interactions of the predictors and the function of time and was confirmed for all significant covariates.

For all analyses, two-sided p-values < 0.05 were considered statistically significant. All analyses were performed using SAS Software, release 9.4 (SAS Institute, Cary, NC).

Results

In the period from February 25, 2020 to April 12, 2021, data from 1040 hospitalized patients with COVID-19 were recorded in the Covid BioB database (<https://covidbiob/covid19/home.php>). This study included 648 hospitalized patients who met the inclusion criteria and were successfully matched: 216 cases and 432 controls. The median age was 64 years (54–77), 60.2% were male. Patient characteristics at hospital admission according to RDV treatment status are detailed in Table 1. As cases and controls were matched based on age, sex, and P/F ratio at admission, there was no difference in these characteristics among the two groups. In addition, there were no significant differences between the two groups in terms of prevalence of comorbidities (with the exception of chronic kidney disease) or in body mass index values.

Patients were admitted to the hospital after a median of 8 (5–11) days from the onset of symptoms: 7 (4–9) days for cases and 8 (5–11) days for controls ($p = 0.009$). Among the cases, the drug was administered 1 (0–3) day after hospitalization. Only 43 patients (20.9%) started RDV ≤ 5 days from symptom onset. Length of hospitalization was similar between the two groups, but there were some important differences in COVID-19 therapies, as detailed in Table 2. These findings were related to the different timing of hospitalization between cases and controls. The majority of controls were hospitalized before September 2020 (during “the first wave”) when RDV, corticosteroids, and low molecular weight heparins were not yet recommended by international guidelines.

Treatment with RDV was well-tolerated. The frequency of acute kidney injury was 1.4% among cases and 1.9% among controls ($p = 0.759$). Arrhythmias were detected in 3.2% of the cases and 3.3% of the controls ($p = 1.000$). Cases and controls did not have significantly different transaminases or serum creatinine values.

Table 1 Patient Characteristics, Respiratory Function, and Laboratory Values at Admission for Hospitalized COVID-19 Patients, Stratified by Remdesivir Treatment Status

Variable	Category	Overall (n = 648)	Remdesivir (n = 216)	No Remdesivir (n = 432)	p-value
Age, years		64 (54–77)	63 (54–77)	64 (54–76)	0.817
Sex	Female	258 (39.8%)	86 (39.8%)	172 (39.8%)	1.000
Ethnicity	White	552 (85.2%)	174 (80.6%)	378 (87.5%)	0.025
Body mass index, kg/m ²		26.9 (24.4–30.5)	27.1 (24.2–31.0)	26.8 (24.5–30.1)	0.55
Duration of symptoms, days		8 (5–11)	7 (4–9)	8 (5–11)	0.009
Number of comorbidities*	0	228 (35.2%)	80 (37%)	148 (34.3%)	0.921
	1	188 (29%)	61 (28.2%)	127 (29.4%)	
	2	124 (19.1%)	40 (18.5%)	84 (19.4%)	
	≥3	108 (16.7%)	35 (16.2%)	73 (16.9%)	
Neurological disorder/dementia		48 (7.4%)	19 (8.8%)	29 (6.7%)	0.343
Cardiovascular disease		177 (27.3%)	58 (26.9%)	119 (27.5%)	0.926
Cancer		91 (14%)	33 (15.3%)	58 (13.4%)	0.549
Diabetes		106 (16.4%)	30 (13.9%)	76 (17.6%)	0.260
Hypertension		305 (47.1%)	97 (44.9%)	208 (48.1%)	0.436
Chronic kidney disease		24 (3.7%)	2 (0.9%)	22 (5.1%)	0.008
PaO ₂ /FiO ₂ , mmHg	>200	302 (46.6%)	99 (45.8%)	203 (47%)	0.802
	≤200	346 (53.4%)	117 (54.2%)	229 (53%)	
PaO ₂ /FiO ₂ , mmHg	>100	473 (73%)	162 (75%)	311 (72%)	0.416
	≤100	175 (27%)	54 (25%)	121 (28%)	
Alanine aminotransferases, U/L		33.5 (22–53)	32 (21–51.5)	35 (23–56)	0.179
Creatinine, mg/dL		0.93 (0.78–1.15)	0.92 (0.76–1.09)	0.95 (0.78–1.19)	0.016
Lactic acid dehydrogenase, U/L		328.5 (265–422)	320.5 (261–408)	337.5 (265–425)	0.176
Lymphocyte cell count, 10 ⁹ /L		1 (0.7–1.3)	0.9 (0.65–1.2)	1 (0.7–1.4)	0.002
C-reactive protein, mg/L		55.35 (26.3–110.2)	50.5 (25.5–96.05)	60.7 (26.9–116.8)	0.125
D-dimer, µg/L		0.89 (0.51–1.69)	0.79 (0.42–1.42)	1.05 (0.61–1.99)	<0.0001
Interleukin-6, pg/mL		26.8 (9.3–53.9)	21.2 (6.5–39.9)	36.1 (13.7–69.6)	0.0001

Notes: *The following comorbidities were considered: malignancies, diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, moderate or severe liver disease, moderate or severe renal disease, neurological disease (chronic neurological disorder, dementia), and rheumatic diseases.

Abbreviation: PaO₂/FiO₂, arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂).

SARS-CoV-2 Clearance

The median number of nasopharyngeal swabs performed on each patient during follow-up was 8 (4–14). VC within 30 days following discharge was reached by 490 patients (75.6%). Of these 490 patients, 54.7% achieved VC during hospitalization, while the remaining 45.3% reached VC during the post-discharge follow-up period. Median time to VC was 25 (16–34) days.

Overall, time to VC was not significantly different between cases and controls ($p = 0.519$) (Figure 1A). However, time to VC was different when considering both RDV treatment status and age. The proportion of patients who achieved

Table 2 Characteristics of Hospitalization and Concomitant Pharmacological Therapy That Was Administered to Patients, Stratified by Remdesivir Treatment Status

Variable	Overall (n = 648)	Remdesivir (n = 216)	No Remdesivir (n = 432)	p-value
Hospitalization after September 1, 2020	305 (47%)	178 (82%)	127 (29%)	<0.0001
Length of hospitalization (days)	15 (9–26)	14 (9–23)	15 (9–28)	0.702
Use of anakinra	121 (18.7%)	46 (21.3%)	75 (17.4%)	0.240
Use of tocilizumab	24 (3.7%)	2 (0.9%)	22 (5.1%)	0.007
Use of corticosteroids	354 (54.6%)	183 (84.7%)	171 (39.6%)	<0.0001
Use of low molecular weight heparin	466 (71.9%)	186 (86.1%)	280 (64.8%)	<0.0001
Use of antibiotics	503 (77.6%)	151 (69.9%)	352 (81.5%)	0.001

VC by 40 days following hospitalization was 89.5% among cases aged ≤65 years, 86.7% among controls aged ≤65 years, 74.5% among cases aged >65 years, and 75.6% among controls aged >65 years (p=0.007) (Figure 1B).

A significant finding was also observed when considering both RDV treatment status and P/F values at admission. The proportion of patients who achieved VC by 40 days following hospitalization was 87% among cases with a P/F >200 mmHg, 88.7% among controls with a P/F >200 mmHg, 82.1% among cases with a P/F ≤200 mmHg, and 75.3% among controls with ≤200 mmHg (p = 0.007) (Figure 1C).

Our multivariate analysis showed that a younger age (aHR = 0.990, 95% CI 0.983–0.998 per every 10 years, p = 0.009) and baseline PaO₂/FiO₂ >200 mmHg (aHR = 1.275, 95% CI 1.029–1.579; p = 0.026) were associated with VC (Table 3). RDV treatment status did not affect VC (aHR = 0.963, CI 0.747–1.241; p = 0.768).

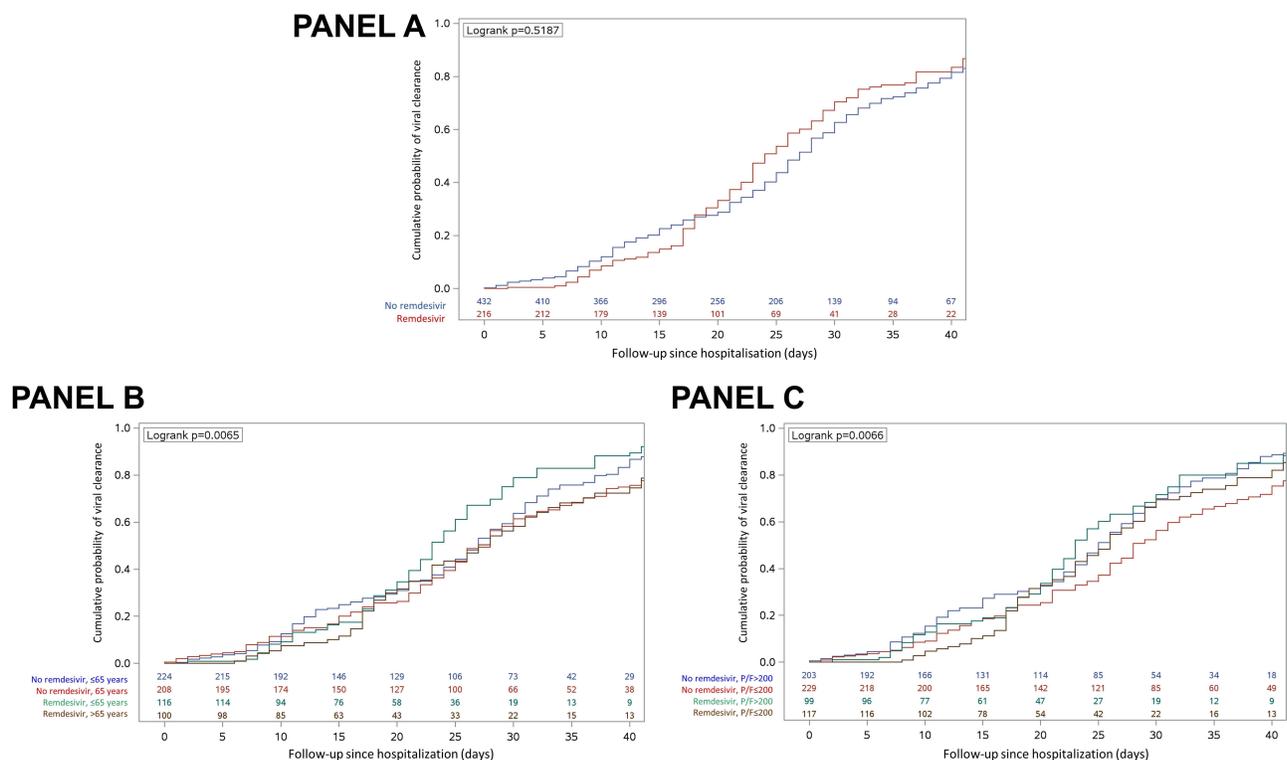


Figure 1 (A) Time to viral clearance, stratified by remdesivir treatment status. (B) Time to viral clearance, stratified by remdesivir treatment status and age (≤65 years vs >65 years). (C) Time to viral clearance, stratified by remdesivir treatment status and PaO₂/FiO₂ at admission (≤200 mmHg vs >200 mmHg).

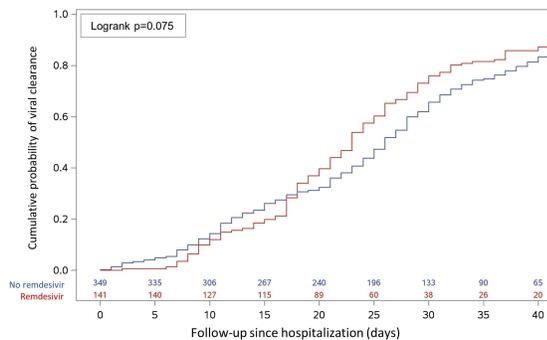
Table 3 Multivariable Cox Proportional Hazard Model: Factors Associated with Viral Clearance

Characteristics	Category	Adjusted Hazard Ratio	95% Hazard Ratio Confidence Interval		p-value
Age	Per every 10-years	0.990	0.983	0.998	0.009
Sex	Female vs male	0.931	0.765	1.134	0.479
Presence of comorbidities*	Yes vs no	0.858	0.690	1.066	0.167
Baseline PaO ₂ /FiO ₂ ratio	> 200 vs ≤ 200 mmHg	1.275	1.029	1.579	0.026
Baseline total lymphocyte cell count	>1 vs ≤1 10 ⁹ cells/L	0.947	0.773	1.161	0.602
Baseline C-reactive protein value	>55.2 vs ≤ 55.2 mg/L	0.906	0.733	1.119	0.360
Baseline lactate dehydrogenase value	>330 vs ≤330 U/L	1.026	0.828	1.270	0.816
Use of at least 1 biological drug**	Yes vs no	0.811	0.640	1.029	0.085
Use of remdesivir	Yes vs no	0.963	0.747	1.241	0.768
Use of steroids	Yes vs no	1.300	0.978	1.654	0.126

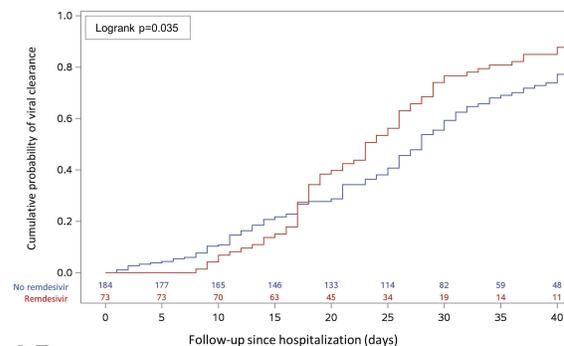
Notes: *The following comorbidities were considered: malignancies, diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, moderate or severe liver disease, moderate or severe renal disease, neurological disease (chronic neurological disorder, dementia), and rheumatic diseases. **Category of biological drugs include anakinra, tocilizumab, sarilumab.

Among patients who achieved VC during the follow-up period, overall time to VC was similar among cases and controls (p = 0.075) (Figure 2A). However, RDV treatment status was associated with a higher probability of VC among patients with a P/F admission value ≤200 mmHg (p = 0.035) (Figure 2B), age ≤65 years (p = 0.050) (Figure 2C), and

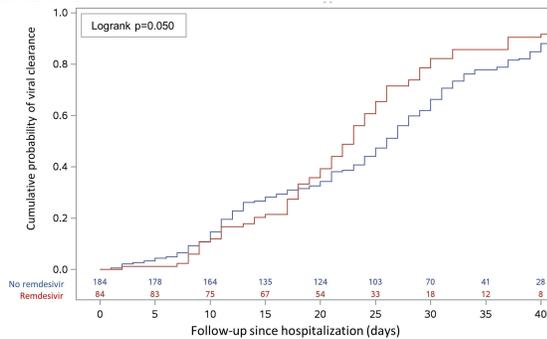
Panel A



Panel B



Panel C



Panel D

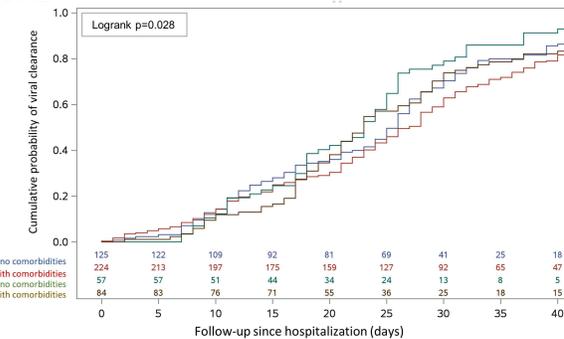


Figure 2 Time to viral clearance among those who achieved viral clearance, stratified by remdesivir treatment status. (A) Overall. (B) Among patients with a P/F ratio ≤200 mmHg at admission. (C) Among patients aged ≤65 years. (D) Among patients with and without comorbidities. The following comorbidities were considered: malignancies, diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, moderate or severe liver disease, moderate or severe renal disease, neurological disease (chronic neurological disorder, dementia), and rheumatic diseases.

Table 4 Cycle Threshold (Ct) Values, Stratified by Remdesivir Treatment Status, in Patients Who Achieved Viral Clearance

Variable	Overall (n=648)	Remdesivir (n=216)	No Remdesivir (n=432)	p-value
First Ct	30.1 (26.0–34.0)	29.8 (26.2–33.6)	30.1 (25.9–34.3)	0.609
	n = 384	n = 178	n = 206	
Last Ct (within 30 days from discharge)	34.1 (29.2–36.5)	34.0 (29.1–36.6)	34.1 (29.5–36.4)	0.831
	n = 97	n = 52	n = 45	
Change in Ct	5.8 (1.7–8.7)	6.7 (3.0–9.7)	3.5 (–0.9–8.2)	0.015
	n = 83	n = 49	n = 34	
Time interval (days) between first and last Ct	14 (9–19)	15 (10–22)	13.0 (9–19)	0.207

patients without comorbidities ($p = 0.028$) (Figure 2D). Among patients who achieved VC, cases experienced a greater decrease in Ct values than controls (Table 4), although, this finding should be interpreted with caution due to the small number of observations.

Discussion

In our study, we evaluated the effect of RDV on VC timing in COVID-19 hospitalized patients for 1 month following hospital discharge. We observed that a younger age and a higher PaO₂/FiO₂ ratio on admission were associated with VC. This is consistent with previous studies that identified older age and disease severity as risk factors for delayed VC.^{25–28} Zou et al²⁹ showed that the viral RNA shedding pattern of patients with COVID-19 was similar to that of patients with influenza, whereby nasopharyngeal viral clearance was delayed in patients at advanced ages and with more severe forms of disease. In addition, older patients are more often affected by comorbidities. Previous work²⁷ has also shown an association between the presence of comorbidities and slower SARS-CoV-2 clearance. However, RDV treatment status was not associated with VC. Other studies have reported similar findings.^{19,21,22,30} This could reflect the timing of RDV treatment, which may be administered too late to effectively impact VC. Wong et al³¹ demonstrated that early remdesivir treatment was associated with a significantly greater increase in Ct values on day 7. In our study, RDV was administered, on average, 8 days after symptom onset with only 43 patients (20.9%) starting it ≤ 5 days from symptom onset.

It is possible that RDV better exerts its antiviral activity in the lower respiratory tract than in the upper respiratory tract. This has been previously reported in preclinical trials⁶ where the administration of intravenous or inhaled remdesivir significantly reduced viral burdens in a nonhuman primate model of SARS-CoV-2 infection in both bronchoalveolar lavage fluid and respiratory tract tissues but not in nasal or throat swabs specimens.³² A complicating factor in our study concerned different concomitant therapies between cases and controls. Steroids were administered to more cases than controls. These drugs have been associated with potential delayed VC,³³ although this evidence has been questioned by different studies.^{30,34}

Interestingly, there was an observed effect of RDV on VC in some patient subgroups. When we considered use of RDV and either age or respiratory impairment at admission (the two factors with a significant effect on time to VC), we observed significant difference between groups. Younger RDV patients and RDV patients with a P/F at admission of ≤ 200 mmHg derived more benefits in terms of time to VC. These findings were confirmed when only patients who achieved VC during follow-up were considered. In these patients, treatment with RDV was associated with a decreased time to VC in those with a P/F ≤ 200 mmHg at admission and ≤ 65 years of age, when compared to controls. Younger patients have a more efficient immune response compared to older patients.³⁵ In this population characterized by a lower nasopharyngeal viral load and faster viral decay,³⁶ the antiviral activity of RDV may further facilitate VC.

Disease severity has been described as a possible risk factor for delayed VC and higher nasopharyngeal viral loads.³⁷ In these patients, at high risk of clinical progression and delayed VC, our findings may increase the strength of recommendation for the use of RDV treatment.

Strengths and Limitations

The main strengths of this study include the large number of patients who were evaluated and a relatively long follow-up period. However, there are several limitations. First, we cannot exclude a potential selection bias given that included patients needed to have at least two nasopharyngeal swabs. This criterion excluded patients who exhibited a more aggressive disease course and died within a few days of hospital admission. Second, viral sequencing was not routinely performed and, therefore, it was not possible to assess the likely effects of SARS-CoV-2 variants of concern (VOCs) on the timing of VC and RDV efficacy. However, given that RDV targets the highly conserved viral RNA-dependent polymerase, it is likely that RDV maintains efficacy against emerging SARS-CoV-2 VOCs.³⁸ Indeed, recent data has shown that RDV remains active against the SARS-CoV-2 Omicron variant and other VOCs.³⁹ Third, Ct values and their relative changes were available only for a minority of patients, which may limit the generalizability of our findings. Finally, most controls were hospitalized before September 1, 2020, while most cases were hospitalized afterward this date. To mitigate this discrepancy, the multivariate analysis that assessed the predictive factors for VC was stratified by date of hospitalization (“first wave” and “second wave”).

Conclusions

In conclusion, overall time to VC was not significantly different between patients who received or did not receive RDV treatment. However, the use of RDV was associated with a benefit concerning time-to-VC in patients younger than 65 years of age and in those with a P/F ratio ≤ 200 mmHg on hospital admission.

COVID-BioB Study Group

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All authors listed in the COVID-BioB study group contributed to the collection and review of the data.

Data Sharing Statement

The datasets used and analyzed during this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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