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

Vincenzo Spagnuolo, Marta Yoarino, Marco Tonelli, Laura Galli, Andrea Poli, Elena Bruzzi, Sara Racca, Nicola Clementi, Chiara Ottolini, Moreno Tresoldi, Patrizia Rovere Querini, Lorenzo Dagna, Alberto Zangrillo, Fabio Cicci, Massimo Clementi, Antonella Castagna

On behalf of the COVID-BioB Study Group

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 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. 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. In particular, different preclinical studies have demonstrated the efficacy of RDV in blocking SARS-CoV-2 infection in human cells and animal models. 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. However, the efficacy of RDV as a therapeutic agent for severe COVID-19 is still in question; 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.\textsuperscript{10} In hospitalized patients, the first stage of the Adaptive COVID-19 Treatment Trial (ACCT-1)\textsuperscript{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.\textsuperscript{12–17} 

In contrast, the SOLIDARITY and DisCoVeRy trials\textsuperscript{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.\textsuperscript{20} In addition, evidence for the effect of RDV on SARS-CoV-2 viral clearance (VC) is scarce and contradictory. Different studies\textsuperscript{19,21,22} have shown that the use of RDV is not associated with nasopharyngeal viral load changes, while other studies\textsuperscript{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\textsubscript{2})/fraction of inspired oxygen (FiO\textsubscript{2}) value (± 10 mmHg) on admission. The PaO\textsubscript{2}/FiO\textsubscript{2} (P/F) ratio represents the ratio between PaO\textsubscript{2} as determined by arterial blood gas analysis, and the percentage of oxygen supplied (FiO\textsubscript{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 ≤1 × 10^9 cells/mm^3).

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   |
| $\text{PaO}_2/\text{FiO}_2$, mmHg | >200            | 302 (46.6%)       | 99 (45.8%)            | 203 (47%)                | 0.802   |
|                              | ≤200            | 346 (53.4%)       | 117 (54.2%)           | 229 (53%)                |         |
| $\text{PaO}_2/\text{FiO}_2$, 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 (9.3–33.9)   | 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: $\text{PaO}_2/\text{FiO}_2$, arterial partial pressure of oxygen ($\text{PaO}_2$)/fraction of inspired oxygen ($\text{FiO}_2$).

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...
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 PaO\textsubscript{2}/FiO\textsubscript{2} >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).

### 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 PaO\textsubscript{2}/FiO\textsubscript{2} >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 PaO\textsubscript{2}/FiO\textsubscript{2} at admission (≤200 mmHg vs >200 mmHg).
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

**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

**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.
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 PaO$_2$/FiO$_2$ 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 al$^{29}$ 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 work$^{27}$ 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 al$^{31}$ 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 trials,$^6$ 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.

### 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   |
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
Badalucco F1,2, Baiardo Redaelli M1, Baldissera E6, Bigai G2, Boffini N6, Borio G2, Bossolasco S1, Bottanelli M1,2, Calabrò MG2, Calvisi S7, Campochiaro C6, Canetti D1, Canti V3, Castellani J2, Cavalli G2,6, Cavallo L2, Cernuschi M1, Chirullo M1,2, Cilla M6, Cinel E2, Cinque P1, Clemente T1,2, Conte C2, Da Prat V5, Danise A1, De Lorenzo R2, De Luca G6, Dell’Acqua A6, Dell’Acqua R1, Della Torre E6, Della Torre L1, Di Terlizzi G5, Dumea I2, Farolfi F2, Ferrante M2,5, Frangi C2, Gallina G2, Germinario B2, Gianotti N1, Guffanti M1, Hassan H1, Lalla F2, Landoni G7, Lanzillotta M2, Li Voti R2, Mainardi L1,2, Mancini N2,3, Mastrangelo A1,2, Messina E1, Moizo E7, Monardo R1,2, Montagna M2, Monti G7, Morì G1,2, Morsica G1, Muccini C1,2, Nozza S1, Pascali M2, Papaioannou Borjesson R1,2, Patrizi A5, Pieri M7, Ponta G1,2, Prestifilippo D2, Ramirez G2,6, Ranzenigo M1,2, Ripa M1,2, Sapienza J2, Sartorelli S2,6, Seghi P3, Tassan Din C1, Tomelleri A2,6, Turi S7, Uberti-Foppa C1,2.
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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