Remdesivir and Mortality in Patients With Coronavirus Disease 2019

George A. Diaz,1,2,4 Alyssa B. Christensen,2,4 Tobias Pusch,4 Delaney Goulet,5 Shu-Ching Chang,6 Gary L. Grunkemeier,6 Paul A. McKelvey,6 Ari Robicsek,7 Tom French,8 Guilford T. Parsons,9 Glenn Docherty,10 Charles Laurenson,10 Ryan Roper,10 Jennifer Hadlock,9 Cameron J. Cover,9 Brent Footer,9 Philip Robinson,9 Mary Micikas,1,11 Jennifer E. Marfori,4 Charlotte Cronenweth,12 Yogavedya Mukkamala,12 Charlotte Cronenweth,12 Yogavedya Mukkamala,12 Jamie Mackiewicz,12 Ekra Rai,12 Martha Dickinson Matson,12 Jodie Davila,12 Justin Rueda,12 Reda Tipton,12 Heather Algren,12 Brittney C. Ward,12 Stephen Malkoski,12 Tyler Gluckman,12 Gregory B. Tallman,12 Henry Arguinichona,12 Terese C. Hammond,12 Steven Standaert,13 Joshua Christensen,12 Jose F. Echaiz,14 Robert Choi,1 Daniel McClung,1 Albert Pacifico,1 Martin Fee,1 Farjad Sarafian,5 William R. Berrington,9,11 and Jason D. Goldman10,11,21

Background. The impact of remdesivir (RDV) on mortality rates in coronavirus disease 2019 (COVID-19) is controversial, and the mortality effect in subgroups of baseline disease severity has been incompletely explored. The purpose of this study was to assess the association of RDV with mortality rates in patients with COVID-19.

Methods. In this retrospective cohort study we compared persons receiving RDV with those receiving best supportive care (BSC). Patients hospitalized between 28 February and 28 May 2020 with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection were included with the development of COVID-19 pneumonia on chest radiography and hypoxia requiring supplemental oxygen or oxygen saturation ≤94% with room air. The primary outcome was overall survival, assessed with time-dependent Cox proportional hazards regression and multivariable adjustment, including calendar time, baseline patient characteristics, corticosteroid use, and random effects for hospital.

Results. A total of 1138 patients were enrolled, including 286 who received RDV and 852 treated with BSC, 400 of whom received hydroxychloroquine. Corticosteroids were used in 20.4% of the cohort (12.6% in RDV and 23% in BSC). Comparing persons receiving RDV with those receiving BSC, the hazard ratio (95% confidence interval) for death was 0.46 (.31–.69) in the univariate model (P < .001) and 0.60 (.40–.90) in the risk-adjusted model (P = .01). In the subgroup of persons with baseline use of low-flow oxygen, the hazard ratio (95% confidence interval) for death in RDV compared with BSC was 0.63 (.39–1.00; P = .049).

Conclusion. Treatment with RDV was associated with lower mortality rates than BSC. These findings remain the same in the subgroup with baseline use of low-flow oxygen.

Keywords. SARS-CoV-2; COVID-19; Mortality; Remdesivir; Standard of Care.

The pandemic of COVID-19 due to severe acute respiratory syndrome coronavirus 2 continues to severely affect communities around the world, and optimal treatments are undefined. Remdesivir (RDV) is an adenosine analogue that inhibits viral RNA–dependent RNA polymerase [1]. In the randomized, double-blinded placebo-controlled Adaptive COVID-19 Treatment Trial (ACTT-1) [2], RDV shortened recovery time. Although this trial was not powered to assess differences in mortality, a strong mortality signal was seen in the prespecified subgroup of patients started on RDV treatment while requiring baseline use of low-flow oxygen. More recently, a study sponsored by the World Health Organization (WHO) [3] suggested no mortality benefit of RDV compared with placebo. In this study, the level of oxygen support was not described in granular detail, potentially masking a mortality benefit when used earlier in the disease course. Olender et al [4] found a mortality benefit to RDV when comparing open-label RDV at some study sites with a matched retrospective cohort of patients from different institutions.
centers, though the effect of baseline disease severity was incompletely explored.

We evaluated the association of RDV with mortality rates in persons with COVID-19 pneumonia while RDV was not the standard of care, before implementation of the Food and Drug Administration (FDA) emergency use authorization (EUA); thus, clinical equipoise existed at the point of prescribing. Hydroxychloroquine (HCQ) was an experimental therapy in widespread use during the study period and was subsequently shown not to affect mortality rates [3, 5–10]. Thus, we assessed the mortality effect after RDV or best supportive care (BSC), including those who received HCQ as part of BSC in the primary analysis.

METHODS

Study Setting
Providence St Joseph Health (PSJH) consists of 51 hospitals in Washington, Oregon, California, Montana, Alaska, New Mexico, and Texas. PSJH was the first health system in the United States to care for a patient with COVID-19 [11] and 14 facilities functioned as study sites for RDV clinical trials [2, 12, 13]. PSJH has a centralized clinical governance structure that updated guidance frequently throughout the pandemic, including appropriate use of supportive care and investigational (RDV) and off-label (HCQ) therapies for COVID-19 (Supplementary Methods).

Patient Population
We reviewed records of all hospitalized patients with an admission date of COVID-19 between 28 February and 29 May 2020. The end date was chosen to coincide with the closure of the Gilead SIMPLE-Severe extension study, when RDV was still investigational. Further use of RDV after this date was via the FDA's EUA per PSJH system guidance and was part of the evolving standard of care. Thus, for the study period, the efficacy of RDV at the point of prescribing was unknown.

We enrolled patients into this retrospective study according to the prospective enrollment criteria used by the Gilead-sponsored SIMPLE-Severe randomized controlled trial (GS-US-540–5773) [12], under which the majority of patients in the PSJH system received RDV. The inclusion and exclusion criteria from SIMPLE-Severe were modified as follows: persons included in this cohort were adults ≥18 years old who were hospitalized for COVID-19 and who had laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection by polymerase chain reaction, chest radiographic evidence of infiltrates suggesting COVID-19 pneumonia, and hypoxia requiring the use of supplemental oxygen or oxygen saturation ≤94% with room air. Patients were excluded from this study if they received an investigational therapy for COVID-19 other than RDV or HCQ, if they received concomitant RDV and HCQ, or if they were pregnant or had multisystem organ failure, severe renal dysfunction (creatinine clearance [CrCl] <30 mL/min), or severe hepatitis (transaminase levels >5 times the upper limit of normal). Patients were enrolled at “time zero” (T0) when meeting all inclusion criteria and no exclusion criteria.

Interventions
Participants in the RDV group received RDV after enrollment in 1 of 4 investigational protocols: the manufacturer (Gilead Sciences) compassionate use program (n = 3) [14], the manufacturer-sponsored SIMPLE-Severe (GS-US-540–5773 and NCT04292899; n = 243) [12], and SIMPLE-Moderate (GS-US-540–5774 and NCT04292730; n = 25) [13] or the National Institutes of Health ACTT-1 (NCT04280705; n = 6) [2]. Nine persons were treated under the FDA EUA. Patients were treated with RDV (200 mg intravenously once and then 100 mg intravenously every 24 hours for a total duration of either 5 or 10 days). Participants receiving BSC were offered supportive therapies, including symptomatic management, supplemental oxygen, supportive ventilation, and other intensive care treatments at the discretion of their treating physicians. To better understand what constituted BSC, we conducted a survey of all hospitals in the study (Supplementary Methods and Supplementary Figure 1). Participants receiving HCQ were dosed using off-label prescribing [15], with the dose, frequency, and duration determined by the attending physician. Most persons received loading dose a 400 mg twice per day, followed by 200 mg twice a day (or 400 mg daily) for a 5-day duration [16].

Statistical Analysis
The primary study end point was overall survival. Vital status was assessed through follow-up encounters for hospitalization or ambulatory appointments (Supplementary Methods and Supplementary Table 1), and patients were censored at the last known alive date. Demographic, comorbid condition, laboratory, treatment, and outcome data were extracted from the electronic medical records via the PSJH electronic data warehouse or by manual record review (Supplementary Table 2). To compare baseline covariates between groups, χ² tests and analysis of variance were performed for categorical and continuous variables, respectively. The primary analysis used a Cox proportional hazards regression to model overall survival between study groups. Baseline patient characteristics were included as fixed effects, and a hospital indicator variable as a random effect (Supplementary Methods, including Supplementary Table 3). To address immortal time bias, the exposure was considered as a time-dependent variable (Supplementary Methods, including Supplementary Figure 2). The Kaplan-Meier method was used to estimate survival. Variables assessed for confounding (Table 1) were selected a priori based on expert opinion (G. A. D., A. B. C., T. P., D. G., and J. D. G.) and were included in the risk-adjusted model if associated with the primary outcome. Based on reviewer
## Table 1. Baseline Characteristics of Cohort

| Characteristic | Total (N = 1138) | RDV (n = 286) | BSC (n = 852) | P Value |
|---------------|------------------|---------------|---------------|---------|
| **Demographics** |                  |               |               |         |
| Age, mean (SD) | 65.4 (16.5)      | 61.4 (16.9)   | 66.8 (16.1)   | <.001   |
| Male sex      | 630 (55.4)       | 162 (56.6)    | 468 (54.9)    | .66     |
| Race          |                  |               |               | .10     |
| White         | 569 (50.0)       | 150 (52.4)    | 419 (49.2)    |         |
| Asian/Pacific Islander | 106 (9.3) | 33 (11.5)    | 73 (8.6)       |         |
| Black/African American | 63 (5.5) | 13 (4.5)     | 50 (5.9)       |         |
| Hispanic/Latino | 284 (25.0) | 57 (19.9)    | 227 (26.6)    |         |
| Other/unknown | 116 (10.2)       | 33 (11.5)     | 83 (9.7)      |         |
| **Ethnicity** |                  |               |               | .02     |
| Hispanic/Latino | 284 (25.0) | 57 (19.9)    | 227 (26.6)    |         |
| Not Hispanic/Latino | 815 (71.6) | 214 (74.8) | 601 (70.5)   |         |
| Other/unknown | 39 (3.4)         | 15 (5.2)      | 24 (2.8)      |         |
| **Comorbid conditions** |            |               |               |         |
| Diabetes      | 258 (22.7)       | 66 (23.1)     | 192 (22.5)    | .91     |
| Dementia      | 324 (28.5)       | 85 (29.7)     | 239 (28.1)    | .64     |
| Hypertension  | 382 (33.6)       | 109 (38.1)    | 273 (32.0)    | .07     |
| Cancer        | 57 (5.0)         | 15 (5.2)      | 42 (4.9)      | .96     |
| MI            | 19 (1.7)         | 5 (1.7)       | 14 (1.6)      | >.99    |
| CHF           | 77 (6.8)         | 13 (4.5)      | 64 (7.5)      | .11     |
| PVD           | 105 (9.2)        | 23 (8.0)      | 82 (9.6)      | .50     |
| CVA/TIA       | 86 (7.6)         | 20 (7.0)      | 66 (7.7)      | .77     |
| CAD           | 87 (7.6)         | 23 (8.0)      | 64 (7.5)      | .87     |
| COPD          | 62 (5.4)         | 12 (4.2)      | 50 (5.9)      | .35     |
| CKD           | 94 (8.3)         | 15 (5.2)      | 79 (9.3)      | .04     |
| Liver disease | 14 (1.2)         | 3 (1.0)       | 11 (1.3)      | .99     |
| PUD           | 4 (0.4)          | 0 (0.0)       | 4 (0.5)       | .56     |
| **Clinical features at admission** |            |               |               |         |
| BMI, median (IQR) | 28.2 (24.3–33.5) | 29.2 (25.1–34.6) | 27.9 (23.9–33.1) | .003 |
| Admission from SNF | 319 (28.0) | 58 (20.3)  | 261 (30.6) | .001 |
| AMS           | 207 (18.2)       | 43 (15.0)     | 164 (19.2)    | .13     |
| DNR status    | 165 (14.5)       | 42 (14.7)     | 123 (14.4)    | >.99    |
| Pulmonary infiltrate | 1056 (92.8) | 264 (92.3) | 792 (93.0)   | .81     |
| Pleural effusion | 96 (8.4) | 17 (5.9)   | 79 (9.3)   | .10     |
| FIB-4, median (IQR) | 2.45 (1.52–3.81) | 2.40 (1.42–3.55) | 2.47 (1.57–3.90) | .11 |
| PSI, median (IQR) | 77 (55–102) | 71 (52–92) | 80 (58–106) | <.001 |
| **WHO-OSS at admission** |            |               |               | .44     |
| 3 (No O₂)     | 416 (36.6)       | 107 (37.4)    | 309 (36.3)    |         |
| 4 (Low-flow O₂) | 656 (57.6) | 168 (58.7) | 488 (57.3)   |         |
| 5 (High-flow O₂) | 48 (4.2) | 8 (2.8)    | 40 (4.7)    |         |
| 6 (Mechanical ventilation) | 18 (1.6) | 3 (1.0)   | 15 (1.8)    |         |
| **WHO-OSS at T0** |            |               |               | .36     |
| 3 (No O₂)     | 210 (18.5)       | 49 (17.1)     | 161 (18.9)    |         |
| 4 (Low-flow O₂) | 850 (74.7) | 223 (78.0) | 627 (73.6)   |         |
| 5 (High-flow O₂) | 54 (4.7) | 9 (3.1)    | 45 (5.3)    |         |
| 6 (Mechanical ventilation) | 24 (2.1) | 5 (1.7)   | 19 (2.2)    |         |
| **Laboratory values, median (IQR)** |            |               |               |         |
| WBC count, ×10⁹/L | 6.58 (5.02–9.00) | 6.25 (4.97–8.28) | 6.70 (5.10–9.10) | .01 |
| ALC, ×10³/L    | 0.90 (0.68–1.00) | 0.90 (0.70–1.00) | 0.90 (0.68–1.00) | .23 |
| Hemoglobin, g/dL | 13.4 (12.1–14.6) | 13.5 (12.2–14.9) | 13.3 (12.0–14.5) | .10 |
| Platelet count, ×10³/L | 199 (157–258) | 197 (157–250) | 200 (157–261) | .52 |
| LDH, IU/L      | 344 (257–439)    | 420 (314–511) | 329 (251–422) | .004 |
| Serum creatinine, mg/dL | 0.91 (0.75–1.17) | 0.89 (0.71–1.08) | 0.94 (0.76–1.20) | .002 |
| CrCl, mL/min   | 96 (63–135)      | 110 (82–147)  | 91.18 (59–131) | <.001 |
| Ferritin, ng/mL | 547 (242–1069)  | 435 (193–786) | 565 (244–1069) | .25 |
| BNP, pg/mL     | 83 (25–297)      | 40 (13–110)   | 91 (30–373)   | <.001 |
feedback, 2 additional variables were added to the multivariable model: corticosteroid use and a term for temporal effect (week of T0). Steroids were assessed as ever use or cumulative dose (Supplementary Methods). Baseline variables were not included in the model if they contributed to a summated score that was included in the model (eg, age is included in the Pneumonia Severity Index [PSI]) [17] and mechanical ventilation status in the WHO ordinal scale score for disease severity [WHO-OSS]) [18].

Subgroup survival analyses stratified by baseline oxygenation status were performed to replicate the analysis from the National Institutes of Health ACTT-1. The mapping of WHO-OSS used in this study to the National Institute of Allergy and Infectious Diseases OSS used in the ACTT-1 trial is given in Supplementary Table 4. Because HCQ had no significant effect on mortality rates in multiple prior studies [3, 5–10], the primary analysis compared those receiving RDV with those receiving supportive care, with or without HCQ, labeling this group BSC. Participants with CrCl of 30–49 mL/min were included in ACTT-1 (with inclusion in the FDA labeling); however, the SIMPLE-Severe trial excluded this population. Thus, we included these patients in our primary analysis and controlled for baseline CrCl ≥ 50 mL/min. We also performed a sensitivity analysis limited to patients with CrCl ≥ 50 mL/min. To augment the findings of the Cox proportional hazards model for overall survival, we conducted mixed effects logistic regression analyses for in-hospital and 30-day mortality rates. All statistical analyses were performed using R software, version 3.6.3 (R Core Team 2020) [19].

RESULTS

Cohort Description

From 28 February to 28 May 2020, a total of 4513 COVID-19 admissions occurred in 3110 unique persons. After application of all inclusion and exclusion criteria (Supplementary Methods), a total of 1138 persons were enrolled in the primary analysis cohort. Of these, 286 received RDV and 852 were treated with BSC, including 400 who received HCQ (Figure 1).

Baseline Data

Demographic and clinical characteristics of patients receiving RDV and BSC are shown in Table 1. Males accounted for 55.4% of patients, and those receiving RDV were younger (mean age [standard deviation [SD], 61.4 [16.9] vs 66.8 [16.1] in the BSC group; P < .001. The cohort was ethnically diverse (50.0% identified as white, 25.0% as Hispanic/Latino, 9.3% Asian or Pacific Islander, 5.5% as black, and 10.2% as other or not reported), with similar distributions between groups. Participants were enrolled from Washington (47.2%), Oregon (8.6%), California (43.5%), Alaska (0.5%), and Montana (0.2%). The most common comorbid conditions were dementia (28.5%), diabetes mellitus (22.7%), and chronic kidney disease (CKD; 8.3%). Comorbid conditions were similar across treatment groups, except for CKD. Only 5.2% of those receiving RDV compared with 9.3% of those receiving BSC had CKD, which follows from the exclusion of persons with low CrCl from receiving RDV, per the SIMPLE-Severe (GS-US-5773) study protocol [12]. Do-not-resuscitate (DNR) status on admission was specified by 14.5% of the cohort, and this was similar between groups. Disease severity according to the WHO-OSS did not differ between groups, but the PSI was higher in those receiving BSC, a difference largely driven by age.

Exposure to Investigational Treatments and Time-Dependent Follow-up

In the RDV group, the mean number of RDV doses (SD) was 7 (3), and the mean (SD) cumulative dose was 803 (279) mg.

Data Sharing

The study protocol, statistical code, and data set may be shared with approved individuals on request and through a written agreement with the authors.
The mean (SD) time from admission to RDV was 1.6 (1.4) days, and the mean time from T0 to RDV, 1.1 (1.3) days. As expected before publication of RECOVERY study results [20], corticosteroid use was predominantly prednisone or methylprednisone rather than dexamethasone. During the COVID-19 admission, a corticosteroid was administered in 232 persons, with any use in 12.6% of the RDV group and 23.0% of the BSC group. Conversion to prednisone equivalents and summing of total corticosteroid exposure also showed more use in the BSC group than in the RDV group (Supplementary Table 5).

The mean (SD) length of stay for the first hospitalization after COVID-19 diagnosis was 10.5 (10.8) days. The total follow-up time was a median (interquartile range) of 47.9 (10.7–159.0) days. In the entire study population, 266.8 patient-years of follow-up from T0 occurred. Data on contribution to follow-up time in the time-dependent model is given in Supplementary Table 6. Vital status (death or alive) was ascertained in 1138 (100%) of persons at hospital discharge, 847 (74.4%) at 30 days after T0, and in 728 (64.0%) at 60 days after T0 (Supplementary Figures 3 and 4). Individual patient courses are graphically represented in Figure 2, which represents the data used to construct the unadjusted time-dependent model.

**Survival Outcomes**

During cohort follow-up, death occurred in 206 of 1138 persons (18.1%), with 169 deaths occurring in the hospital, 182 by 30 days, and 195 by 60 days after T0. Among treatment groups, death during follow-up occurred in 33 of 286 persons receiving RDV, 78 of 400 receiving HCQ, and 95 of 452 of receiving supportive care alone. The unadjusted Kaplan-Meier survival rates
were 89.8% (RDV), 78.9% (HCQ), 79.8% (supportive care alone) at 30 days, and 87.3% (RDV), 77.8% (HCQ), and 78.0% (supportive care alone) at 60 days (Figure 3).

In the mixed effects Cox proportional hazards regression, using treatment arm as a time-dependent covariate and accounting for the hierarchical effects of hospital, the hazard ratio (HR) (95% confidence interval [CI]) in univariate analysis was 0.46 (.31–.69; P < .001) for RDV compared with BSC. In the risk-adjusted model, controlling for WHO-OSS, PSI, DNR status, race/ethnicity, body mass index, CrCl <50 mL/min, dementia, hypertension, D-dimer level, absolute lymphocyte count, any history of corticosteroid use, hospital site, and temporal effect, the HR (95% CI) was 0.60 (.40–.90; P = .01) for RDV compared with BSC (Table 2 and Supplementary Figure 5). Using cumulative corticosteroid dose in prednisone equivalents instead of any receipt of corticosteroids in the model did not change the estimates. To disentangle any effect of HCQ, we also separated the BSC group into supportive care alone and HCQ only (Supplementary Results). Kaplan-Meier estimates are shown in Figure 3.

In a sensitivity analysis, restricted to persons with CrCl ≥50 mL/min, 14 and 167 persons were dropped from the RDV and BSC groups, respectively. The HR (95% CI) for death was 0.58 (.37–.92; P = .02) with the univariate analysis and 0.66 (.42–1.04; P = .07) with the risk-adjusted model, for RDV compared to BSC.

Subgroup analyses stratified by baseline disease severity are presented in Table 2. Of the 1138 enrolled persons, the baseline WHO-OSS was 3 (no oxygen) in 210 persons, 4 (low-flow oxygen) in 850, and 5–6 (high-flow oxygen or mechanical ventilation) in 58. Mortality was 87.1%, 87.8%, and 88.1%, respectively, at 30 days and 84.8%, 87.1%, and 88.7%, respectively, at 60 days (Figure 3). In univariate analysis, the HR (95% CI) was 0.48 (.33–.71; P < .001) for RDV compared with BSC for WHO-OSS 3, 0.61 (.43–0.87; P = .007) for WHO-OSS 4, and 0.60 (.38–0.94; P = .03) for WHO-OSS 5–6.

In the risk-adjusted model, the HR (95% CI) was 0.71 (.48–1.05; P = .08) for RDV compared with BSC for WHO-OSS 3, 0.68 (.41–1.12; P = .14) for WHO-OSS 4, and 0.66 (.38–1.15; P = .17) for WHO-OSS 5–6.
ventilation) in 78. In univariate analysis, the HR (95% CI) for death was 0.44 (.28–.70; P < .001) for RDV compared with BSC for persons with a baseline WHO-OSS of 4 (low-flow oxygen). With the multivariable risk-adjusted model, the HR (95% CI) for death was 0.63 (.39–1.00; P = .049) for RDV compared with BSC for those with a baseline WHO-OSS of 4 (low-flow oxygen).

To account for possible misclassification due to inclusion of blinded participants from the ACTT-1 study, an additional sensitivity analysis excluded these 6 participants. The HR (95% CI) for death in RDV group compared with the BSC group was 0.42 (.28–.64; P < .001) in univariate analysis and 0.58 (.38–.90; P = .02) in the risk-adjusted model. When analyses were limited to those with a baseline WHO-OSS of 4, the HR (95% CI) was 0.42 (.27–.68; P < .001) in univariate analysis and 0.59 (.37–.95; P = .03) in the risk-adjusted model.

In-Hospital and 30-Day Mortality Rates

The mortality rates were 14.9% in the hospital, 16.0% at 30 days, and 17.1% for 60 days. The odds ratio (95% CI) was 0.61 (.34–1.07) for the in-hospital mortality rate and 0.56 (.32–.97) for the 30-day mortality rate in the RDV group compared with the BSC group. The results and conclusion from this secondary analysis were consistent with those from primary mixed effects Cox regression with time-dependent treatment analysis for overall survival.

Table 2. Mixed Effects Cox Proportional Hazards Regression Analysis

| Analyses (RDV vs BSC) | Patients, No. | Deaths, No. | Hazard Ratio (95% CI) | P Value |
|-----------------------|---------------|-------------|----------------------|---------|
| Whole cohort          |               |             |                      |         |
| Univariate analysis   | 1138          | 206         | 0.46 (.31–.69)       | <.001   |
| Risk-adjusted analysis | 1106         | 197         | 0.60 (.40–.90)       | .01     |
| Subgroup analysis stratified on baseline disease severity | | | | |
| WHO-OSS                |               |             |                      |         |
| 3 (No O₂)              | 210           | 15          | 0.14 (.02–1.12)      | .06     |
| 4 (Low-flow O₂)        | 850           | 160         | 0.44 (.28–.70)       | <.001   |
| 5–6 (HFNC, IMV)        | 78            | 31          | 0.68 (.23–2.06)      | .50     |
| WHO-OSS                |               |             |                      |         |
| 3 (No O₂)              | 202           | 13          | 1.10 (.10–12.77)     | .94     |
| 4 (Low-flow O₂)        | 827           | 154         | 0.63 (.39–1.00)      | .049    |
| 5–6 (HFNC, IMV)        | 77            | 30          | 0.72 (1.19–2.70)     | .63     |

Abbreviations: BSC, best supportive care; CI, confidence interval; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation; RDV, remdesivir; WHO-OSS, World Health Organization ordinal scale score for disease severity.

*aModels use treatment arm as a time-dependent covariate and account for the hierarchical effects of hospital location of treatment across the Providence St Joseph Health system. Analyses are given for the whole cohort and subgroup analysis stratified on baseline disease severity, as defined by the WHO-OSS.

*bRisk-adjusted model includes adjustment for 12 risk factors including pneumonia severity index, WHO-OSS, do-not-resuscitate status, race/ethnicity, body mass index, creatinine clearance <50 mL/min, dementia, hypertension, D-dimer level, absolute lymphocyte count, any corticosteroid use, and a term for temporal effect.
DISCUSSION

It is urgently necessary to define optimal treatment of COVID-19. Results from the ACTT-1 trial suggested a mortality benefit in patients receiving RDV who require low-flow oxygen at baseline, not in other subgroups [2]. The WHO Solidarity trial suggested no mortality benefit for treatment with RDV in patients receiving oxygen, but the study did not stratify by baseline disease severity status using a granular ordinal scale [3], potentially masking the benefit in the patient population requiring low-flow oxygen.

Our study assessed all-cause mortality rates among 1138 patients treated with RDV or BSC during an era when RDV was not the standard of care. In multivariable Cox regression analysis, the mortality rate (hazard function) was reduced by 40% in those treated with RDV compared with BSC. The analyses presented here largely support the findings of the ACTT-1 trial, which showed that RDV reduced mortality rates when started in patients with COVID-19 pneumonia with a baseline need for low-flow oxygen but before further disease progression. Similarly, the association with reduced mortality rates seen in our entire population (WHO-OSS, 3–6) remained the same for the low-flow oxygen group (WHO-OSS, 4). Physiologically, the intervention seems effective during the virological phase, and before significant hyperinflammation develops, as described for the dynamic and bimodal COVID-19 disease process [21].

The current study has numerous strengths. The study cohort represented a diverse patient population from multiple centers in a large health system in the western United States. To mimic a randomized trial as closely as possible with a retrospective study, several study design or statistical methods were used, including simulated enrollment at T0. A time-dependent Cox regression model was designed to mitigate immortal time bias. Results are robust against a number of alternative analyses, including logistic regression for set time points. In addition, an analysis excluding 6 ACTT-1 participants was robust to the primary study findings. A survey of standard of care across the participating centers did not reveal substantial variation between hospitals with or without access to RDV. Of interest, PSIs were calculated based on electronically and manually extracted data strongly correlated with mortality rate, confirming value as a predictor of mortality rates with COVID-19 (Supplementary Figure 6). The mortality rate in our overall cohort was 16.0% at 30 days, which is comparable to rates in other reports: 9%–28% (Supplementary Table 7). The concordance of our mortality estimates with results from these different settings, including other studies of RDV [2, 4], strengthens the generalizability of our findings.

The study also has several important limitations. First, the study groups were heterogeneous: patients receiving BSC were older, had higher baseline PSIs, were more likely to have CKD, and were more likely to be admitted from SNF than those receiving RDV. This may reflect both confounding by indication (perhaps patients judged more likely to die were less likely to be offered investigational therapy) and the challenge of comparing clinical trial enrollees with other patients (CKD was an RDV study exclusion criterion). In a sensitivity analysis limited to those with normal renal function, the association is attenuated and not statistically significant. This could be due to reduced power; alternatively, CKD could be considered a measured covariate, which confounds the primary finding.

Despite attempts to control for confounding, measured or unmeasured confounders may remain. Exclusion of persons receiving concomitant COVID-19 treatments helps to improve generalizability and reduce confounding by these other treatment modalities, although experimental treatments administered at other hospitals before arrival at our centers may not have been recorded. The duration of symptoms before treatment initiation was not assessed, perhaps missing an opportunity to assess the proper timing of drug intervention given the importance of initiating antivirals early in the disease course [2]. While assessment of adverse events was beyond the scope of this analysis, we believe that our primary end point encompasses the most important safety data contained in adverse event reporting, namely, mortality rate data. While results of a retrospective cohort cannot supplant RCT results, these data can help answer a question for which RCT data are incomplete—namely, whether RDV use is associated with reduced mortality rates in hospitalized patients with COVID-19.

In summary, in a retrospective cohort study we used a time-dependent Cox proportional hazards regression with multivariable adjustment to control for key risk factors including hospital effects and to account for immortal time bias among patients treated with the investigational therapies RDV and HCQ. We show that RDV treatment was associated with a survival advantage compared with BSC. These findings remain the same for the subgroup with baseline requirement for low-flow supplemental oxygen, a result consistent with those in the ACTT-1 trial. Further research studies of RDV in routine clinical use are required to further confirm these results.

Notes

Acknowledgments. We would like to acknowledge the patients included in this study and the caregiver teams across the Providence St Joseph Health (PSJH) network. We also recognize the contributions of the following individuals to the conduct of the parent trials: Myung Seon Song, PharmD, Kasey Rubin, PharmD, Scott King, PharmD, Alexandre Croceau, PharmD, Emily Fox, PharmD, Claude Tonnerre, MD, David Christiansen, MD, Marco Lorio, MD, Brian York, MD, Anna Ursales, MD, Marilyn Birchman, RN, MSN, Jerome Differding, MPH, Keeley Heredia, Dean Rocco, Kathleen Sanders, Courtney Bohland, Rebecca Watson, Babita Singh, Shaundai Valdez, Allison Everett, Adel Islam, Julie Wallick, Sephren Barrow, Charlene Boisjolte, RN, Stephanie Johnson, Julia Karr, Clementine Chalal, Octavia Graham, Joshua Mark, PharmD, Imran A. Mohamedi, MD, Rachel N. Plotinsky, MD, Brian A. Kendall, MD, Nicholas L. Stucky, MD, Ronald J Dworkin, MD, Amy M. Dechet, MD, Justin S. Jin, MD, Wendi K. Drummond, MD, Matlin Sader, ARNP, Margo Badman, ARNP, and Michael Bolton, MD, PhD. We thank Sophia Humphreys, PharmD (PSJH Pharmacy Clinical Services), Adam Corson, MD, and Harry Peled, MD.

Michael Bolton, MD, PhD. We thank Sophia Humphreys, PharmD (PSJH Pharmacy Clinical Services), Adam Corson, MD, and Harry Peled, MD.

Remdesivir and Mortality in COVID-19 • CID 2022;74 (15 May) • 1819
References

1. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020; 295:4773–9.

2. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19—final report. N Engl J Med 2020; 383:1813–26.

3. Pan H, Peto R, Henao-Restrepo AM, et al; WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19—interim WHO Solidarity Trial results. N Engl J Med 2021; 384:497–511.

4. Olender SA, Perez KK, Go AS, et al. Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care. Clin Infect Dis 2021; 73:e4166–74.

5. Horby P, Mafham M, Linsell L, et al; RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020; 383:2030–40.

6. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild to moderate Covid-19. N Engl J Med 2020; 383:2041–52.

7. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020; 382:2411–8.

8. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323:2495–502.

9. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med 2020; 173:623–31.

10. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ 2020; 369:m1849.

11. Holshue ML, DeBolt C, Lindquist S, et al; Washington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020; 382:928–36.

12. Goldman JD, Lye DCB, Hui DS, et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020; 383:1827–37.

13. Spinner CD, Gottlieb RL, Criner GJ, et al; GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020; 324:1048–57.

14. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020; 382:2327–36.

15. US Food and Drug Administration. “Off-label” and investigational use of marketed drugs, biologics, and medical devices. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices. Accessed 8 December 2020.

16. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020; 71:732–9.

17. Fine MJ, Aasle TL, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336:243–50.

18. World Health Organization. WHO R&D blueprint, novel coronavirus: COVID-19 therapeutic trial synopsis. Available at: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master__Protocol_synopsis_Final_18022020.pdf. Accessed 8 December 2020.

19. R Core Team. R: A language and environment for statistical computing. Version 3.6.1. Vienna, Austria: R Foundation for Statistical Computing, 2019. https://www.r-project.org/. Accessed 8 December 2020.

20. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 2021; 384:693–704.

21. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020; 39:405–7.