Remdesivir and Mortality in Patients With Coronavirus Disease 2019

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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

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, χ^2 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
	Patients by Treatment Group, No. (%)[a]			
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 O_2)	416 (36.6)	107 (37.4)	309 (36.3)	
4 (Low-flow O_2)	656 (57.6)	168 (58.7)	488 (57.3)	
5 (High-flow O_2)	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 O_2)	210 (18.5)	49 (17.1)	161 (18.9)	
4 (Low-flow O_2)	850 (74.7)	223 (78.0)	627 (73.6)	
5 (High-flow O_2)	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, ×10⁹/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, ×10⁹/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

Table 1. Continued

Characteristic	Total (N = 1138)	RDV (n = 286)	BSC (n = 852)	P Value
		Patients by Treatment Group, No. (%)[a]		
Procalcitonin, ng/mL	0.10 (0.00–0.23)	0.07 (0.00–0.19)	0.10 (0.00–0.23)	.15
CRP, mg/L	16.5 (7.0–56.2)	16.1 (6.3–45.0)	16.7 (7.3–57.4)	.40
AST, U/L	40 (27–58)	40 (30–55)	40 (27–59)	.69
ALT, U/L	28 (19–46)	30 (20–49)	28 (18–44)	.09
CrCl ≥50 mL/min	957 (85.8)	272 (96.1)	685 (82.2)	<.001
D-dimer level				.02
Normal (≤0.5 ng/mL)	868 (76.3)	235 (82.2)	633 (74.3)	
Moderate (0.51–1.0 ng/mL)	104 (9.1)	23 (8.0)	81 (9.5)	
High (>1.0 ng/mL)	166 (14.6)	28 (9.8)	138 (16.2)	

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AMS, amyotrophic lateral sclerosis; AST, aspartate transaminase; BMI, body mass index; BNP, brain natriuretic peptide; BSC, best supportive care; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRP, C-reactive protein; CVA, cardiovascular Accident; DNR, do-not-resuscitate; FIB-4, Fibrosis-4 index; IQR, interquartile range; LDH, lactose dehydrogenase; MI, myocardial infarction; O₂, oxygen; PSI, pneumonia severity index; PUD, peptic ulcer disease; PVD, peripheral vascular disease; RDV, remdesivir; SD, standard deviation; SNF, skilled nursing facility; T0, time zero; TIA, transient ischemic attack; WBC, white blood cell; WHO-OSS, World Health Organization ordinal scale score for disease severity.

[a]Data represent no. (%) of patients unless otherwise specified. The time frame is at admission for all variables, except where otherwise specified.

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].

Human Subjects Protection
This study was approved by the PSJH Institutional Review Board and granted a waiver of informed consent.

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.

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.
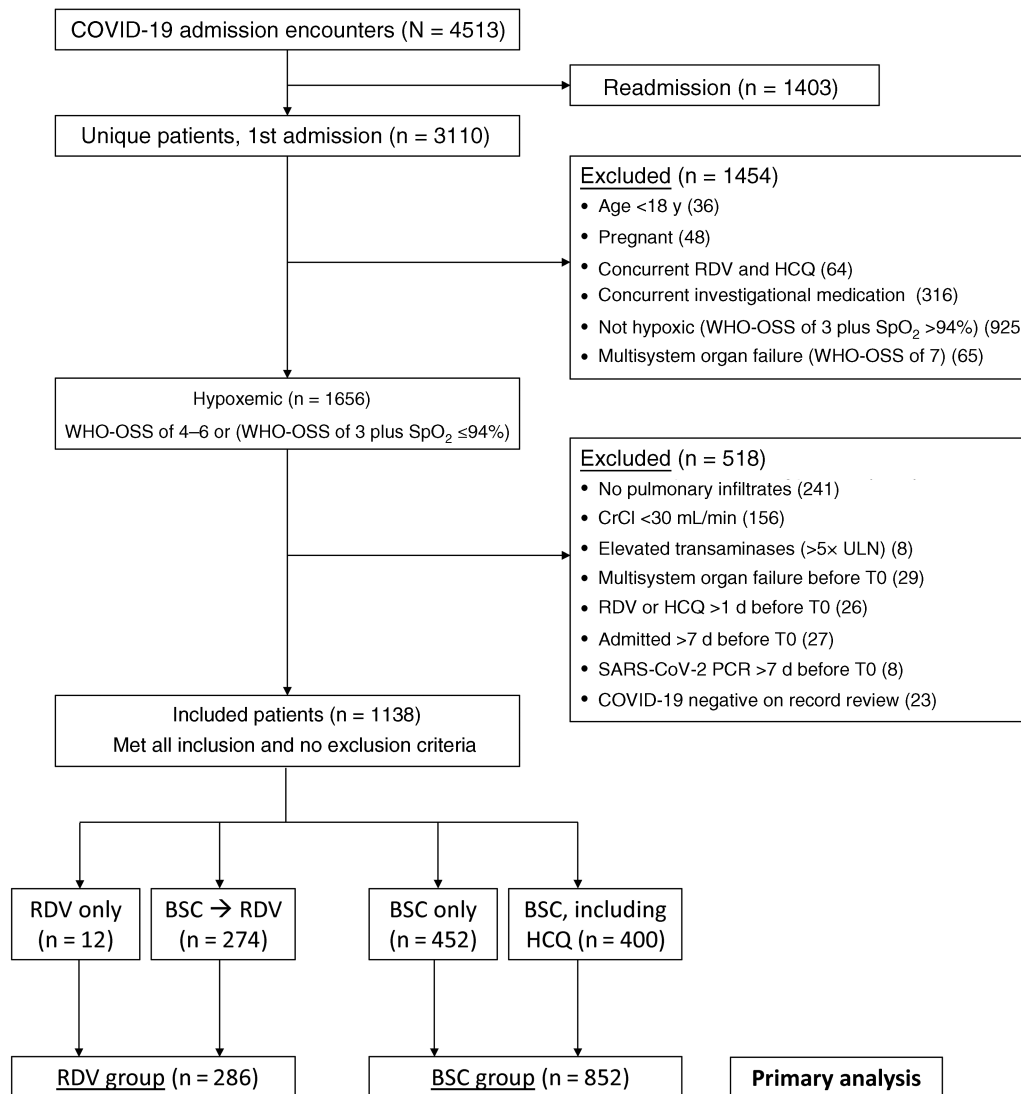
Figure 1. Study enrollment diagram. Abbreviations: BSC, best supportive care; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; PCR, polymerase chain reaction; RDV, remdesivir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO$_2$, oxygen saturation; ULN, upper limit of normal; WHO-OSS, World Health Organization ordinal scale score for disease severity.

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
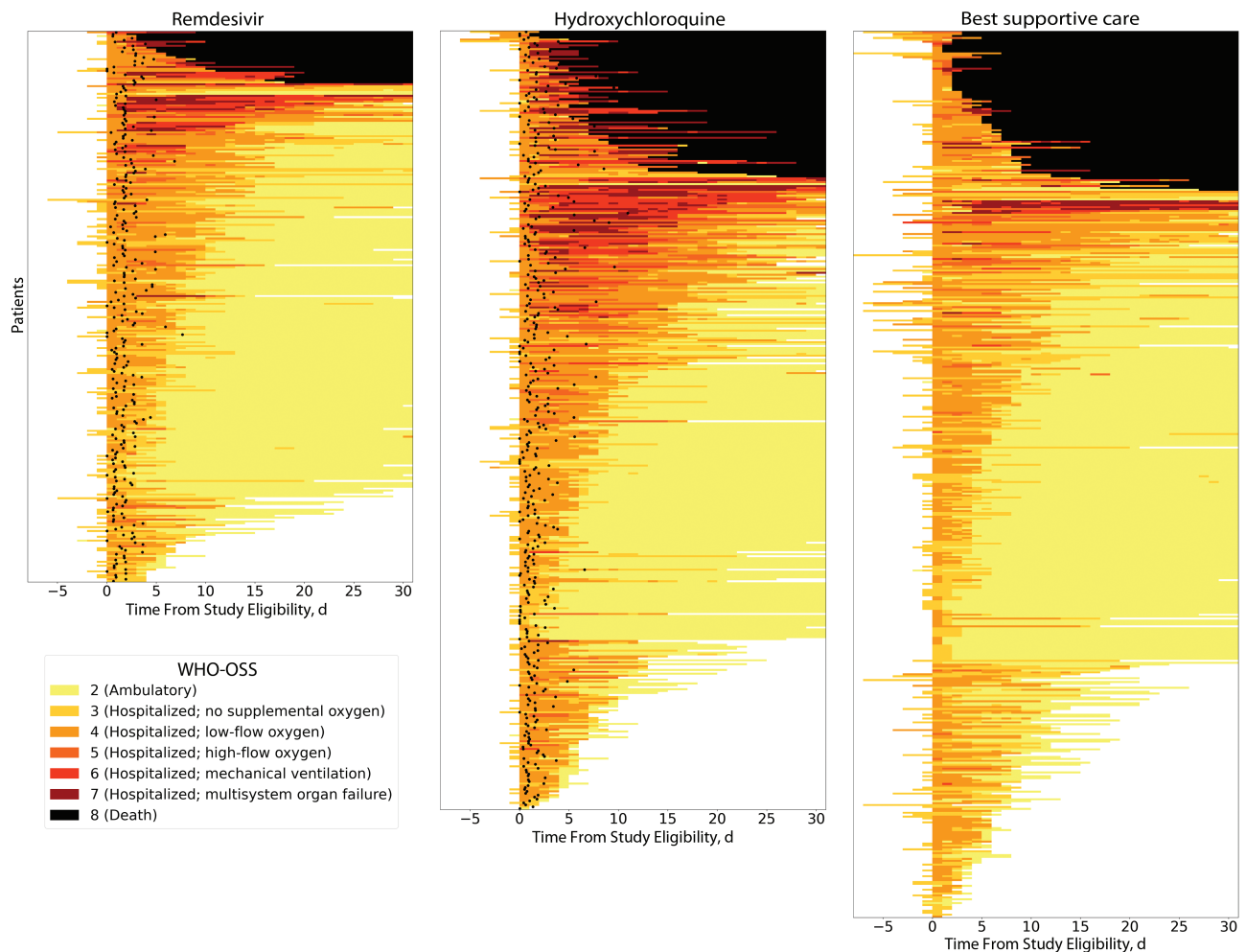
Figure 2. Individual patient course by study group. Swimmers plots represent clinical course for entire study cohort. Patients are included in the groups for remdesivir (RDV) or hydroxychloroquine (HCQ) if they received ≥1 dose of RDV or HCQ, respectively, and included in the group for best supportive care (BSC) if they received neither. First doses of RDV are HCQ is indicated by black dots. Within in each group, rows represent the clinical course for an individual patient, shown by the daily World Health Organization ordinal scale score for disease severity (WHO-OSS), captured as the maximum score for each calendar day. The last observation after hospitalization is carried forward to the next in-person encounter, except for patients lost to follow-up, represented in white for missing. Missing data within the hospitalization (n = 175 of 12 354 days) is carried forward from the most recent observation. Participants are ordered by vital status (dead or alive), and within each group, by descending total WHO-OSS, summed over the 30-day interval.

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
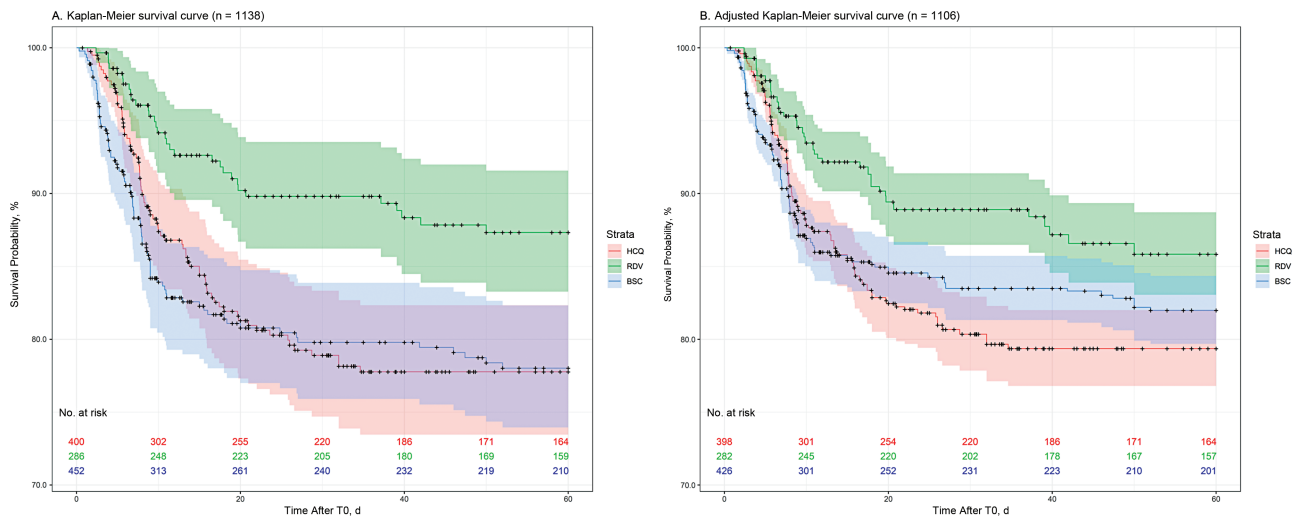
Figure 3. Unadjusted (*A*) and adjusted (*B*) Kaplan-Meier survival curves comparing all-cause mortality rates in hospitalized patients with coronavirus disease 2019 pneumonia treated with remdesivir (RDV), hydroxychloroquine (HCQ), and best supportive care (BSC). Twenty-two patients were excluded from adjusted Kaplan-Meier survival analyses owing to missingness of the risk-adjusted factors. Abbreviation: WHO-OSS, World Health Organization ordinal scale score for disease severity.

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[a]

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[b]	1106	197	0.60 (.40–.90)	.01
Subgroup analysis stratified on baseline disease severity				
Univariate analysis by WHO-OSS				
3 (No O$_2$)	210	15	0.14 (.02–1.12)	.06
4 (Low-flow O$_2$)	850	160	0.44 (.28–.70)	<.001
5–6 (HFNC; IMV)	78	31	0.68 (.23–2.06)	.50
Risk-adjusted analysis by WHO-OSS[b]				
3 (No O$_2$)	202	13	1.10 (.10–12.77)	.94
4 (Low-flow O$_2$)	827	154	0.63 (.39–1.00)	.049
5–6 (HFNC; IMV)	77	30	0.72 (.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.

[a]Models 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.

[b]Risk-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, but 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.

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