Remdesivir and Mortality in Patients with COVID-19

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Summary: From an early retrospective cohort of hospitalized COVID-19 patients, remdesivir use is associated with lower mortality compared to best supportive care. The effect remains the same for the subgroup of patients requiring low flow oxygen at baseline, similar to the ACTT-1 results.

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Abstract

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

Methods: In this retrospective cohort study we compared persons receiving RDV to persons receiving best supportive care (BSC). Patients hospitalized between 2/28/20 – 5/28/20 with laboratory confirmed SARS-CoV-2 infection were included when they developed COVID-19 pneumonia on chest radiography, and hypoxia requiring supplemental oxygen or SpO2 ≤ 94% on 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 effects for hospital.

Results: 1,138 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). In persons receiving RDV compared to those receiving BSC the HR (95%CI) for death was 0.46 (0.31 – 0.69) in the univariate model, p<0.001 and 0.60 (0.40 – 0.90) in the risk-adjusted model, p=0.014. In the sub-group of persons with baseline use of low-flow oxygen, the HR (95%CI) for death in RDV compared to BSC was 0.63 (0.39 – 1.00), p=0.049.

Conclusion: Treatment with RDV was associated with lower mortality compared to 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

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Introduction:

The pandemic of COVID-19 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to severely affect communities around the world and optimal treatments are undefined. RDV is an adenosine analog which inhibits viral RNA-dependent RNA polymerase [1]. In the randomized, double-blinded placebo-controlled trial ACTT-1 [2] RDV shortened recovery time. While this trial was not powered to assess mortality, a strong mortality signal was seen in the pre-specified sub-group of patients started on RDV 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 to 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 mortality benefit to RDV when comparing open-label RDV at some study sites to 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 in persons with COVID-19 pneumonia in the time period when RDV was not the standard-of-care, prior to implementation of the 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.[3, 5-10] Thus, we assessed mortality effect after RDV or best supportive care (BSC) including those who received HCQ, as part of BSC in the primary analysis.

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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 U.S. 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 which updated guidance frequently throughout the pandemic, including appropriate use of supportive care, and investigational (RDV) and off-label (HCQ) therapies for COVID-19 (**supplemental methods**).

Patient Population:

We reviewed records of all hospitalized patients with an admission date of COVID-19 between 2/28/20 and 5/29/20. 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-U.S.-540-5773) [12], under which the majority of patients in the PSJH system received RDV. The inclusion / 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, had laboratory-confirmed SARS-CoV-2 infection by PCR, evidence on chest radiography for infiltrates suggesting COVID-19 pneumonia, and hypoxia requiring the use of supplemental oxygen or SpO2 ≤ 94% on 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 multisystem organ failure, severe renal dysfunction (creatinine clearance (CrCl) < 30 mL/min), severe hepatitis (transaminase levels > 5 times the upper limit of normal) or pregnancy were present. 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 one of four investigational protocols. These included: the manufacturer (Gilead Sciences, Inc) compassionate use program (n=3) [14], manufacturer-sponsored SIMPLE- Severe (GS-US-540-5773, NCT04292899; n=243) [12], and SIMPLE- Moderate (GS-US-540-5774, NCT04292730; n=25) [13], or the NIH Adaptive COVID-19 Treatment Trial (ACTT-1, NCT04280705; n=6) [2]. Nine persons were treated under the FDA EUA. Patients were treated with RDV 200mg IV once and then 100mg IV every 24 hours for a total duration of either 5 or 10 days. Participants who received BSC were offered supportive therapies including symptomatic management, supplemental oxygen, supportive ventilation, and other intensive care

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treatments at the discretion of their treating physicians. To better understand what constituted BSC, we conducted a survey of all hospitals in the study (**supplemental methods and Figure S1**). Participants receiving HCQ were dosed via off-label prescribing [15], and had their dose, frequency and duration determined by the attending physician. Most persons received a 400 mg twice per day loading dose followed by 200 mg twice a day (or 400 mg daily) for a 5-day duration [16].

Statistical Analysis:

The primary study endpoint was overall survival. Vital status was assessed via follow-up encounters for hospitalization or ambulatory appointments (**supplemental methods** and **Table S1**), and patients were censored at the last known alive date. Demographic, comorbidity, laboratory, treatment, and outcome data were extracted from the electronic medical records via the PSJH electronic data warehouse or by manual chart review (**Table S2**). To compare baseline covariates between groups, chi-squared tests and analysis of variance (ANOVA) 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 (**supplemental methods**, including **Table S3)**. To address immortal time bias, the exposure was considered as a time-dependent variable (**supplemental methods**, including **Figure S2**). Kaplan Meier method was used to estimate survival. Variables assessed for confounding (**Table 1**) were selected *a priori* based on expert opinion (G.D., A.C., D.G., T.P. and J.G.), and were included in the risk-adjusted model if associated with the primary outcome. Based on reviewer 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 (**supplemental methods)**. Baseline variables were not included in the model if the variable contributed to a summated score which was included in the model, e.g. age is in Pneumonia Severity Index (PSI) [17], and mechanical ventilation status is in WHO-ordinal severity score (WHO-OSS) [18].

Subgroup survival analyses stratified by baseline oxygenation status were performed to replicate the analysis from NIH ACTT-1. The mapping of WHO-OSS used in this study to the NIAID-OSS used in the ACTT-1 trial is given in **Table S4**. Since HCQ had no significant effect on mortality in multiple prior studies [3, 5-10], the primary analysis compared those receiving RDV to those receiving supportive care, with or without HCQ, and labeling this group BSC. Participants with CrCl 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 limiting to CrCl ≥ 50 mL/min. To augment the findings of the Cox PH model for overall survival, we conducted mixed effects logistic regression analyses for in-hospital, and 30-day mortality. All statistical analyses were performed using R software, version 3.6.3 (R Core Team 2020) [19].

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Human Subjects Protection:

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

Results:

Cohort Description:

From 2/28/20 – 5/28/20, a total of 4,513 COVID-19 admissions occurred in 3,110 unique persons. After applying all inclusion and exclusion criteria (**supplemental methods**), n=1,138 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 (SD) age 61.4 (16.9) compared to 66.8 (16.1) in the BSC group, $p < 0.001$. The cohort was ethnically diverse, with 50.0% identifying as Caucasian, 25.0% as Hispanic/Latino, 9.3% Asian or Pacific Islander, 5.5% Black and 10.2% as other or not reported, with a similar distribution 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 comorbidities were dementia (28.5%), diabetes mellitus (22.7%), and chronic kidney disease (CKD, 8.3%). Comorbidities were similar across treatment groups except CKD. Only 5.2% of those receiving RDV compared to 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 was similar between groups. Disease severity by the World Health Organization ordinal scale score (WHO OSS) was not different between groups, but the pneumonia severity index (PSI) was higher in those receiving BSC, largely driven by age.

Exposure to Investigational Treatments and Time-Dependent Follow-up:

In the RDV group, the mean (SD) number of RDV doses was 7 (3); mean (SD) cumulative dose was 803mg (279mg). The mean (SD) times from admission to RDV was 1.6 (1.4) days and from T0 to RDV was 1.1 (1.3) days. As expected prior to publication of RECOVERY,[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 total corticosteroid exposure also showed more use in the BSC group compared to RDV group (**Table S5**).

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Mean (SD) length of stay (LOS) for the first hospitalization after COVID-19 diagnosis was 10.5 (10.8) days. Total follow-up time was a median (IQR) 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 **Table S6**. Vital status (death or alive) was ascertained in 1,138 (100%) of persons at hospital discharge, 847 persons (74.4%) at 30 days after T0, and in 728 persons (64.0%) at 60 days after T0 (**Figures S3 and S4**). Individual patient course is 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 1,138 persons (18.1%), 169 of which occurred in-hospital. 182 deaths occurred by 30 days and 195 by 60 days after T0. Among treatment groups, mortality during follow-up occurred in 33 of 286 persons receiving RDV, 78 of 400 persons receiving HCQ, and 95 of 452 of persons receiving supportive care alone. Unadjusted Kaplan-Meier survival was 89.8% (RDV), 78.9% (HCQ), 79.8% (supportive care alone) at 30 days, and 87.3% (RDV), 77.8% (HCQ), 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 co-variate and accounting for the hierarchical effects of hospital, the hazard ratio (95%CI) in univariate analysis was 0.46 (0.31 – 0.69), $p < 0.001$ for RDV compared to BSC. In the risk-adjusted model, controlling for WHO-OSS, PSI, DNR, race/ethnicity, body mass index (BMI), creatinine clearance (CrCl) < 50 mL/min, dementia, hypertension, d-dimer, absolute lymphocyte count, ever corticosteroid use, hospital site and temporal effect, the HR (95%CI) was 0.60 (0.40 – 0.90), $p = 0.014$ for RDV compared to BSC (**Table 2 and Figure S5**). Using cumulative corticosteroid dose in prednisone equivalents instead of ever 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 (**supplemental results**). Kaplan-Meier estimates are shown in **Figure 3**.

In a sensitivity analysis, restricting to persons with CrCl ≥ 50 mL/min, 14, and 167 persons drop from the RDV and BSC groups, respectively. The HR (95%CI) for death was 0.58 (0.37 – 0.92), $p = 0.02$ in the univariate analysis and 0.66 (0.42 – 1.04), $p = 0.073$ for the risk-adjusted model for RDV compared to BSC.

Sub-group analyses stratified by baseline disease severity are presented in **Table 2**. Of the 1,138 enrolled persons baseline WHO OSS was 3 (no oxygen), 4 (low-flow oxygen) and 5 – 6 (high-flow oxygen or mechanical ventilation) for 210, 850 and 78 persons, respectively. In univariate analysis the HR (95%CI) for death was 0.44 (0.28 – 0.70), $p < 0.001$ for RDV compared to BSC for persons with baseline WHO-OSS 4 (low-flow oxygen). In multivariable risk-adjusted model, the HR (95%CI) for death was 0.63 (0.39 – 1.00), $p = 0.049$ for RDV compared to BSC for persons with baseline WHO OSS 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

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(95%CI) for death in RDV group compared to BSC group was 0.42 (0.28 – 0.64), p <0.001 in univariate analysis, and 0.58 (0.38-0.90), p = 0.015 in the risk-adjusted model. When limiting to those with baseline WHO OSS = 4, the HR (95%CI) was 0.42 (0.27 – 0.68), p <0.001 in univariate analysis, and 0.59 (0.37 – 0.95), p = 0.031 in the risk-adjusted model.

In-Hospital Mortality and 30-day Mortality:

Mortality was 14.9% for hospital discharge, 16.0% for 30-day and 17.1% for 60-day. The odds ratio (OR, 95%CI) was 0.61 (0.34 – 1.07) for in-hospital mortality, and 0.56 (0.32 – 0.97) for 30-day mortality in the RDV group compared to BSC. The results and conclusion from this secondary analysis were consistent with the primary mixed effects Cox regression with time-dependent treatment analysis for the overall survival.

Discussion:

An urgent need exists 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 assesses all-cause mortality among 1,138 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 to BSC. The analyses presented here largely support the findings of the ACTT-1 trial, which showed that RDV reduced mortality when started in patients with COVID-19 pneumonia with baseline need for low-flow oxygen but prior to further disease progression. Similarly, the association with reduced mortality 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].

This 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. In order to mimic a randomized trial as closely as possible with a retrospective study, several study design or statistical methods were employed, including simulated enrollment with "time zero". A time-dependent Cox regression model designed to mitigate immortal time bias. Results are robust against a number of alternative analyses including logistic regression for set time points. Additionally, 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, PSI scores were calculated based on electronically and manually extracted data strongly correlated with mortality, confirming value as a predictor of mortality with COVID-19 (**Figure S6**). Mortality in our overall cohort was 16.0% at 30-days, which is comparable to other reports: 9 – 28% (**Table S7**). Concordance of our mortality estimates with results from

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these different settings, including other studies of remdesivir [2, 4], strengthens the generalizability of our findings.

This study has several important limitations. First, the study groups were heterogeneous: BSC patients were older, had higher baseline PSI scores, were more likely to have CKD and more likely to have DNR order at the time of admission than RDV patients. 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 (chronic kidney disease was an RDV study exclusion criterion). In a sensitivity analysis limiting to those with normal renal function, association is attenuated and not statistically significant. This could be due to reduced power, or 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, though experimental treatments administered at other hospitals prior to arrival at our centers may not have been recorded. 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 endpoint encompasses the most important safety data contained in adverse event reporting, namely, mortality. While results of a retrospective cohort cannot supplant RCT results, these data can help to further understand a topic in which RCT data is incomplete, namely whether remdesivir use is associated with reduced mortality in hospitalized patients with COVID-19.

In summary, in a retrospective cohort study we use 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 of patients treated with the investigational therapies RDV and HCQ. We show that treatment with remdesivir was associated with a survival advantage compared to best supportive care. These findings remain the same for the sub-group 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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Notes:

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Disclaimer

The manufacturer of RDV (Gilead Sciences, Inc.) and the sponsor of ACTT-1 (NIH NIAID) approved the reuse of data for this study, but was not involved in study design, data preparation, data analysis or manuscript preparation.

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Potential Conflicts

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Data Sharing: The study protocol, statistical code, and data set may be shared with approved individuals upon request and through a written agreement with the authors.

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Table 1: Baseline Characteristics of Cohort.

	All (N=1,138)	RDV (n=286)	BSC (n=852)	p-value
Demographics				
Age, mean (SD)	65.4 (16.5)	61.4 (16.9)	66.8 (16.1)	<0.001
Male sex, n (%)	630 (55.4)	162 (56.6)	468 (54.9)	0.663
Race, n (%)				0.103
White/Caucasian	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, n (%)				0.017
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)	
Co-morbidities, n (%):				
Diabetes	258 (22.7)	66 (23.1)	192 (22.5)	0.914
Dementia	324 (28.5)	85 (29.7)	239 (28.1)	0.642
Hypertension	382 (33.6)	109 (38.1)	273 (32.0)	0.071
Cancer	57 (5.0)	15 (5.2)	42 (4.9)	0.956
MI	19 (1.7)	5 (1.7)	14 (1.6)	0.999
CHF	77 (6.8)	13 (4.5)	64 (7.5)	0.111
PVD	105 (9.2)	23 (8.0)	82 (9.6)	0.495
CVA/TIA	86 (7.6)	20 (7.0)	66 (7.7)	0.773
CAD	87 (7.6)	23 (8.0)	64 (7.5)	0.87
COPD	62 (5.4)	12 (4.2)	50 (5.9)	0.353
CKD	94 (8.3)	15 (5.2)	79 (9.3)	0.044
Liver disease	14 (1.2)	3 (1.0)	11 (1.3)	0.991
PUD	4 (0.4)	0 (0.0)	4 (0.5)	0.560
Clinical Features on Admission:				
BMI, median (IQR)	28.2 (24.3 – 33.5)	29.2 (25.1 – 34.6)	27.9 (23.9 – 33.1)	0.003
Admit from SNF, n (%)	319 (28.0)	58 (20.3)	261 (30.6)	0.001
AMS, n (%)	207 (18.2)	43 (15.0)	164 (19.2)	0.131
DNR status, n (%)	165 (14.5)	42 (14.7)	123 (14.4)	0.995

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Pulmonary infiltrate, n (%)	1056 (92.8)	264 (92.3)	792 (93.0)	0.814
Pleural effusion, n (%)	96 (8.4)	17 (5.9)	79 (9.3)	0.102
FIB-4, median (IQR)	2.45 (1.52 – 3.81)	2.40 (1.42 – 3.55)	2.47 (1.57 – 3.90)	0.109
PSI score - median (IQR)	77 (55 – 102)	71 (52 – 92)	80 (58 – 106)	<0.001
WHO OSS at admit, n (%)				0.445
3 (off 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 (mech vent)	18 (1.6)	3 (1.0)	15 (1.8)	
WHO OSS at T0, n (%)				0.361
3 (off 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 (mech vent)	24 (2.1)	5 (1.7)	19 (2.2)	
Laboratory Values, median (IQR):				
WBC (x10^9 cells/L)	6.58 (5.02 – 9.00)	6.25 (4.97 – 8.28)	6.70 (5.10 – 9.10)	0.014
ALC (x10^9 cells/L)	0.90 (0.68 – 1.00)	0.90 (0.70 – 1.00)	0.90 (0.68 – 1.00)	0.23
Hemoglobin (g/dL)	13.4 (12.1 – 14.6)	13.5 (12.2 – 14.9)	13.3 (12.0 – 14.5)	0.097
Platelets (x10^9 /L)	199 (157 – 258)	197 (157 – 250)	200 (157 – 261)	0.52
LDH (IU/L)	344 (257 – 439)	420 (314 – 511)	329 (251 – 422)	0.004
Serum Creatinine (mg/dL)	0.91 (0.75 – 1.17)	0.89 (0.71 – 1.08)	0.94 (0.76 – 1.20)	0.002
CrCl at T0 (cc/min)				
median (IQR)	96 (63 – 135)	110 (82 – 147)	91.18 (59 – 131)	<0.001
≥50 mL/min, n (%)	957 (85.8)	272 (96.1)	685 (82.2)	<0.001
Ferritin (ng/mL)	547 (242 – 1069)	435 (193 – 786)	565 (244 – 1069)	0.25
D-Dimer (ng/mL), n (%)				0.016
Normal: ≤ 0.5	868 (76.3)	235 (82.2)	633 (74.3)	
Moderate: 0.51 – 1.0	104 (9.1)	23 (8.0)	81 (9.5)	
High: > 1.0	166 (14.6)	28 (9.8)	138 (16.2)	
BNP (pg/mL)	83 (25 – 297)	40 (13 – 110)	91 (30 – 373)	<0.001
Procalcitonin (ng/mL)	0.10 (0.00 – 0.23)	0.07 (0.00 – 0.19)	0.10 (0.00 – 0.23)	0.15
CRP (mg/L)	16.5 (7.0 – 56.2)	16.1 (6.3 – 45.0)	16.7 (7.3 – 57.4)	0.40
AST (U/L)	40 (27 – 58)	40 (30 – 55)	40 (27 – 59)	0.69
ALT (U/L)	28 (19 – 46)	30 (20 – 49)	28 (18 – 44)	0.091

The time frame is at admission for all variables, except where specified.

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Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; BSC = best supportive care; BMI = body mass index; BNP = brain natriuretic peptide; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVD = cardiovascular disease; DNR = do not resuscitate; FIB-4 = Fibrosis-4 Index; IQR = interquartile range; LDH = lactose dehydrogenase; MI = myocardial infarction; PSI = pneumonia severity index; PUD = peptic ulcer disease; PVD = peripheral vascular disease; RDV = remdesivir; SCr = serum creatinine; SD = standard deviation; WBC = white blood cells; WHO OSS = World Health Organization Ordinal Scale Score.

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Table 2: Mixed effects Cox proportional-hazards regression analysis.

Analysis:	Number	Mortality Events	Hazard Ratio (95%CI)	P-value
Whole Cohort:				
Univariate: - **RDV vs BSC**	1,138	206	0.46 (0.31 – 0.69)	<0.001
Risk-adjusted: † - **RDV vs BSC**	1,106	197	0.60 (0.40 – 0.90)	0.014
Sub-group Analysis Stratified on Baseline Disease Severity:				
Univariate: RDV vs BSC - **WHO OSS = 3 (no O2)** - **WHO OSS = 4 (low-flow O2)** - **WHO OSS = 5-6 (HFNC, IMV)**	 210 850 78	 15 160 31	 0.14 (0.02 – 1.12) 0.44 (0.28 – 0.70) 0.68 (0.23 – 2.06)	 0.064 <0.001 0.50
Risk-adjusted † RDV vs BSC - **WHO OSS = 3 (no O2)** - **WHO OSS = 4 (low-flow O2)** - **WHO OSS = 5-6 (HFNC, IMV)**	 202 827 77	 13 154 30	 1.10 (0.10 – 12.77) 0.63 (0.39 – 1.00) 0.72 (0.19 – 2.70)	 0.94 0.049 0.63

Models use treatment arm as a time-dependent co-variate and accounts for the hierarchical effects of hospital location of treatment across the PSJH system. Analyses are given for the whole cohort and sub-group analysis stratified on baseline disease severity, as defined by World Health Organization ordinal scale score (WHO-OSS).

Abbreviations: BSC = best supportive care; RDV = remdesivir; WHO OSS = World Health Organization Ordinal Scale Score.

† Risk-adjusted model includes adjustment for 12 risk factors including PSI, WHO OSS, DNR, race/ethnicity, body mass index (BMI), creatinine clearance (CrCl) < 50 mL/min, dementia, hypertension, d-dimer and absolute lymphocyte count, any corticosteroid use, and a term for temporal effect.

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Figure Legends

Figure 1: Study Enrollment Diagram

Abbreviations: BSC = best supportive care; HCQ = hydroxychloroquine; PCR = polymerase chain reaction; RDV = remdesivir; SpO2 = oxygen saturation; ULN = upper limit of normal; WHO = World Health Organization ordinal scale score.

Figure 2: Individual Patient Course by Study Group. Swimmers Plots representing clinical course for entire study cohort. Patients are included in the groups for Remdesivir (RDV) or Hydroxychloroquine (HCQ) if they received at least one dose of RDV or HCQ, respectively, and included in the group for Best Supportive Care (BSC) if they received neither. First dose of RDV or HCQ is indicated by the black dot. Within in each group, rows represent the clinical course for an individual patient, shown by the daily World Health Organization (WHO) Ordinal Scale Score, captured as maximum score for each calendar day. Last observation after hospitalization is carried forward to the next in-person encounter, unless lost to follow-up and then represented in white for missing. Missing data within the hospitalization (n= 175 / 12,354 days) is carried forward from the most recent observation. Participants are ordered by vital status (death or alive), and within each group, by descending total WHO score, summed over the 30-day interval.

Figure 3: Kaplan-Meier Survival Curves. Unadjusted (A) and adjusted (B) KM survival curves comparing all-cause mortality in those hospitalized patients with COVID-19 pneumonia treated with remdesivir, hydroxychloroquine and best supportive care. 22 patients were excluded from adjusted KM survival analyses due to missingness of the risk-adjusted factors.

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Figure 1

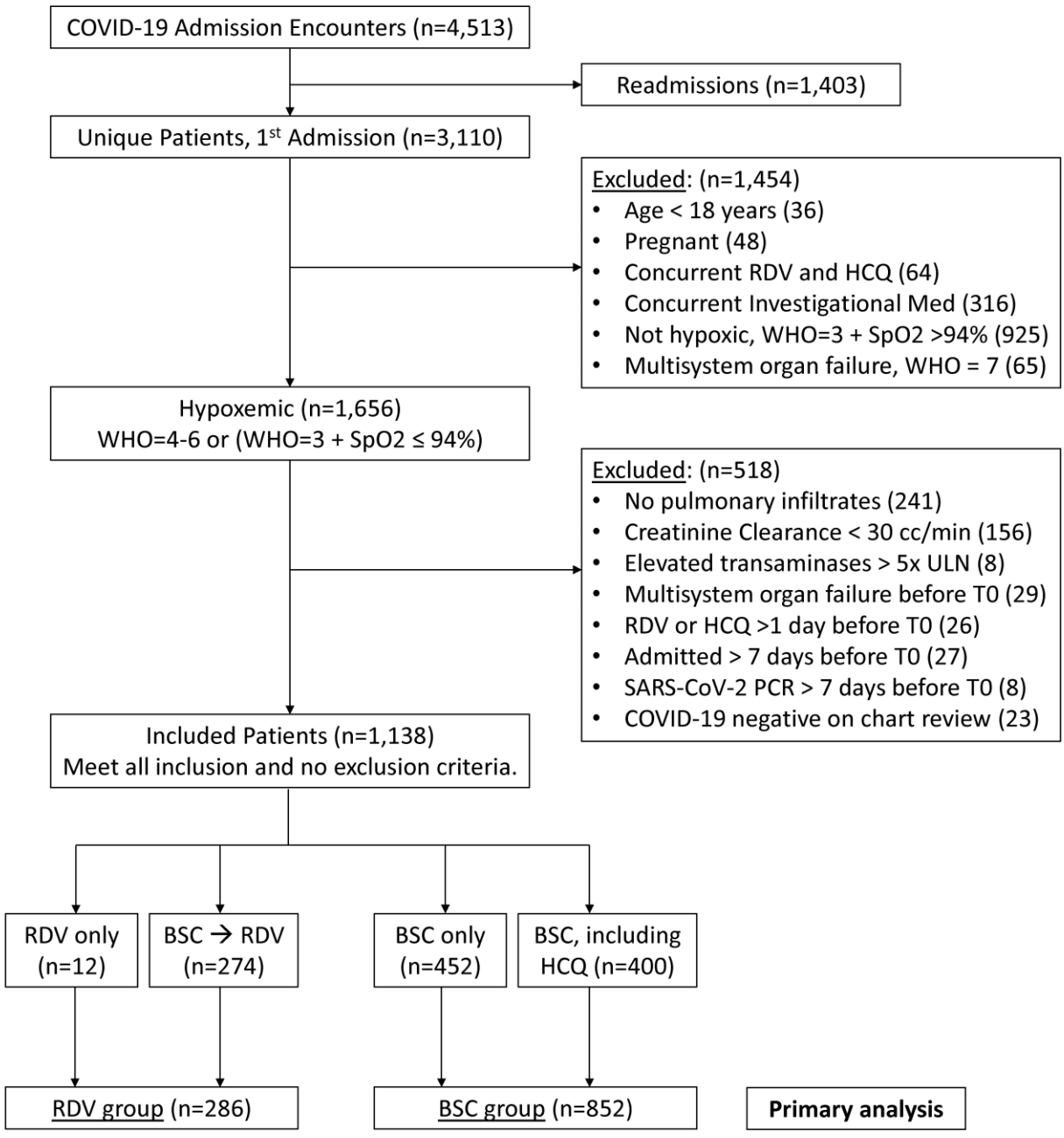

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Figure 2

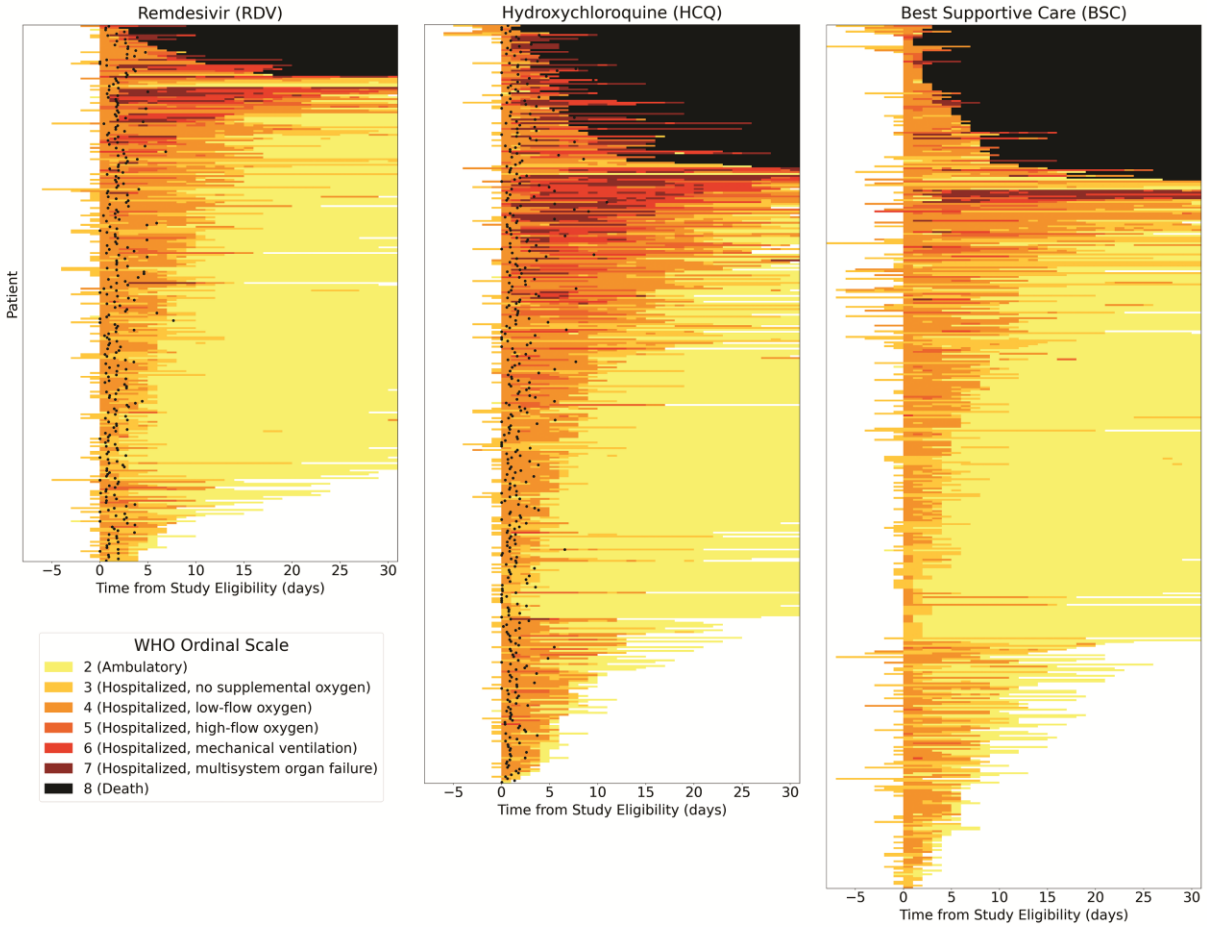

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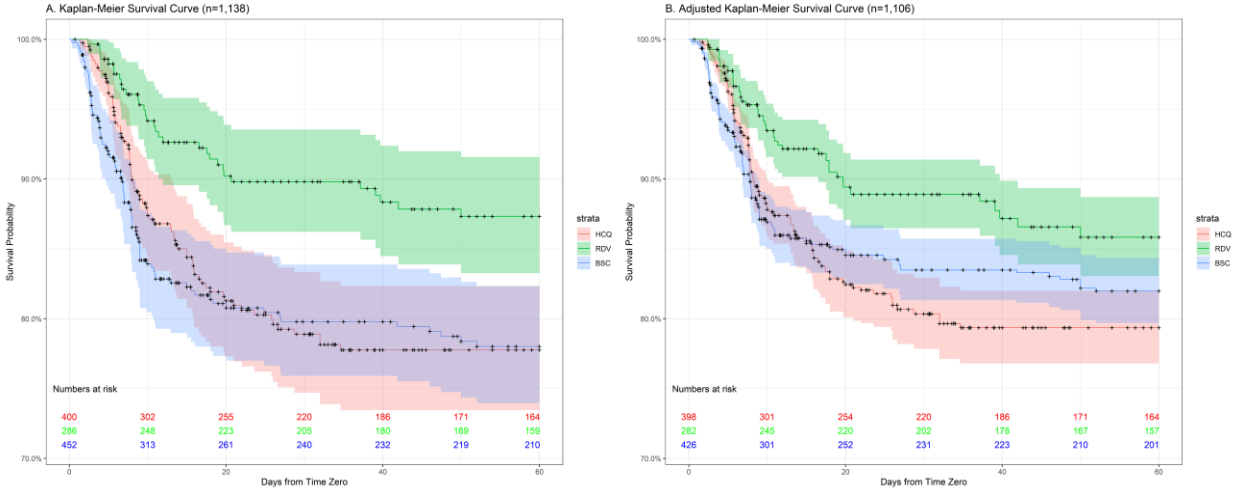
Figure 3



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