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Remdesivir Treatment in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19): A Comparative Analysis of In-hospital All-cause Mortality in a Large Multicenter Observational Cohort

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Background. Remdesivir (RDV) improved clinical outcomes among hospitalized patients with coronavirus disease 2019 (COVID-19) in randomized trials, but data from clinical practice are limited.

Methods. We examined survival outcomes for US patients hospitalized with COVID-19 between August and November 2020 and treated with RDV within 2 days of hospitalization vs those not receiving RDV during their hospitalization using the Premier Healthcare Database. Preferential within-hospital propensity score matching with replacement was used. Additionally, patients were also matched on baseline oxygenation level (no supplemental oxygen charges [NSO], low-flow oxygen [LFO], high-flow oxygen/ noninvasive ventilation [HFO/NIV], and invasive mechanical ventilation/extracorporeal membrane oxygenation [IMV/ECMO]) and 2-month admission window and excluded if discharged within 3 days of admission (to exclude anticipated discharges/transfers within 72 hours, consistent with the Adaptive COVID-19 Treatment Trial [ACTT-1] study). Cox proportional hazards models were used to assess time to 14-/28-day mortality overall and for patients on NSO, LFO, HFO/NIV, and IMV/ECMO.

Results. A total of 28 855 RDV patients were matched to 16 687 unique non-RDV patients. Overall, 10.6% and 15.4% RDV patients died within 14 and 28 days, respectively, compared with 15.4% and 19.1% non-RDV patients. Overall, RDV was associated with a reduction in mortality at 14 days (hazard ratio [95% confidence interval]: 0.76 [0.70–0.83]) and 28 days (0.89 [0.82–0.96]). This mortality benefit was also seen for NSO, LFO, and IMV/ECMO at 14 days (NSO: 0.69 [0.57–0.83], LFO: 0.68 [0.80–0.77], IMV/ECMO: 0.70 [0.58–0.84]) and 28 days (NSO: 0.80 [0.68–0.94], LFO: 0.77 [0.68–0.86], IMV/ECMO: 0.81 [0.69–0.94]). Additionally, HFO/NIV RDV group had a lower risk of mortality at 14 days (0.81 [0.70–0.93]) but no statistical significance at 28 days.

Conclusions. RDV initiated upon hospital admission was associated with improved survival among patients with COVID-19. Our findings complement ACTT-1 and support RDV as a foundational treatment for hospitalized COVID-19 patients.

Keywords. COVID-19; remdesivir; comparative effectiveness research; mortality; hospitalization.

Several pharmacologic agents have been evaluated as treatment options for coronavirus disease 2019 (COVID-19) [1–7]. Remdesivir (RDV) was the first antiviral fully approved by the US Food and Drug Administration and conditionally authorized by the European Medicines Agency for treatment of hospitalized patients with COVID-19 following the National Institute of Allergy and Infectious Diseases-sponsored Adaptive COVID-19 Treatment Trial (ACTT-1) supporting reduced time to recovery and progression among people prescribed with RDV [8–13]. ACTT-1 was not powered to demonstrate mortality difference, and the placebo-controlled portion was discontinued early because of manifest efficacy for the primary endpoint [8]. Despite this, ACTT-1 showed a trend toward improved mortality in the overall population as well as a statistically significant impact in patients on low-flow oxygen (LFO) in a post hoc analysis [8]. The Solidarity trial did not find a significant differences in mortality for RDV vs non-RDV patients; however, a trend toward mortality benefit was identified in nonventilated patients as well as in overall patients [14]. Meta-analyses summarizing clinical trial data

have since demonstrated higher rates of discharge and recovery and a significant reduction in mortality for subgroups of nonventilated patients requiring oxygen at baseline but no significant reduction in mortality in overall patients [15–18]. However, propensity-matched analyses of patients treated with RDV as part of the SIMPLE trial for severe COVID-19 (GS-US-540-5773) vs contemporaneously treated patients in hospitals without access to RDV suggested both a recovery and a mortality benefit associated with RDV [19, 20].

Several observational studies provide additional evidence relating to safety and effectiveness of RDV in treatment of COVID-19 [19, 21–26]. In these studies, RDV use was associated with faster clinical improvement (5 vs 7 days) [24, 25]; shorter duration of mechanical ventilation (5 vs 11 days) [23]; increased probability of hospital discharge (83% vs 59%) [23] and 14-day recovery (odds ratio: 0.38, 95% confidence interval (CI): 0.22-0.68) compared with standard of care [19]. Findings relating to long-term mortality have been inconsistent [22–26]. One study reported improved mortality over an average follow-up of 52 days [26] and although 3 studies found a numerically lower risk of mortality at 28 days, these findings were not statistically significant [22–24]. The lack of statistical significance may reflect small sample sizes. A further limitation of existing studies is that they were conducted using data from the early phase of the pandemic when treatment protocols at local and national levels were variable and rapidly evolving.

We conducted a study using one of the largest, geographically representative COVID-19 hospitalization datasets in the United States. The objective of this study was to compare 14- and 28-day mortality among hospitalized patients with COVID-19 with and without RDV treatment.

METHODS

Study Design and Data Source

This was a retrospective, comparative effectiveness cohort study using data from the Premier Healthcare Database, which is a large US hospital-based database that captures diagnosis and procedure codes, medications, and costs per day relative to admission for approximately 20% of all hospitalizations occurring across 45 states and Washington, DC. However, actual dates and time stamps are not provided to ensure patient privacy; hence, all baseline variables are examined within first 2 days of hospitalization.

Study Population

The study included adult (≥18 years) patients hospitalized August 1, 2020–November 30, 2020 with a primary or secondary discharge diagnosis of COVID-19 (International Classification of Diseases, 10th revision, Clinical Modification: U07.1). Laboratory confirmation of COVID-19 was not feasible in the database. However, the accuracy of International Classification

of Diseases, 10th revision, Clinical Modification code U07.1 has been previously validated in the Premier Healthcare Database as a specificity of 99.04% and sensitivity of 98.01% [27]. Because not all hospitals consistently bill for oxygen supply or devices, particularly LFO, it is possible that the group with no supplementary oxygen (NSO) could include patients who received some level of oxygen that was not billed but instead subsumed in the room charge. To minimize this limitation and permit a clear classification of the NSO group, only those patients from hospitals that reported charges for supplemental oxygen such as LFO for at least 1 patient were included in the NSO group (defined as no supplemental oxygen charge in hospitals that demonstrably charge for supplemental oxygen). Only first admissions occurring during the study period were included.

Patients were excluded from the study population for the following criteria: pregnant; length of stay longer than 100 days to reduce likelihood of hospitalization because of other health conditions; incomplete data; transferred to or from another hospital; transferred from a hospice; elective procedures; discharged or died during baseline period. Patients who received RDV through a clinical trial or who were first administered RDV after the baseline period were also excluded. Figure 1 presents the study consort diagram.

RDV patients were those administered with at least 1 dose of RDV in the first 2 days of hospitalization, whereas non-RDV users were those who were not administered RDV at any time during hospitalization.

Statistical Analysis

The outcomes were 14-day and 28-day all-cause inpatient mortality (defined as a discharge status of "expired" or "hospice"). Patients were followed after the baseline period (ie, from day 3 of admission) until death or end of study period. Patients who were discharged alive and not into a hospice were censored at 14 and 28 days in the analyses.

Propensity score (PS) methods were used to match patients receiving RDV to those not receiving RDV. PS was estimated using separate logistic regression models for NSO, LFO, high-flow oxygen/noninvasive ventilation (HFO/NIV), and invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) groups at baseline. Variables included in PS models were demographics (age group, sex, race, ethnicity, primary payor), key comorbidities, hospital characteristics, admission from skilled nursing facility, admission month, hospital ward upon admission, other indicators of severity based on admission diagnoses (such as hypoxemia, sepsis, respiratory failure, and pneumonia), and concomitant COVID-19 treatment with anticoagulants, corticosteroids, and convalescent plasma at baseline (Supplementary Table 1). All covariates were retained in the model irrespective of their *P* value. Second-order interaction terms were tested and retained in the model only if they were statistically significant ($P < .05$).
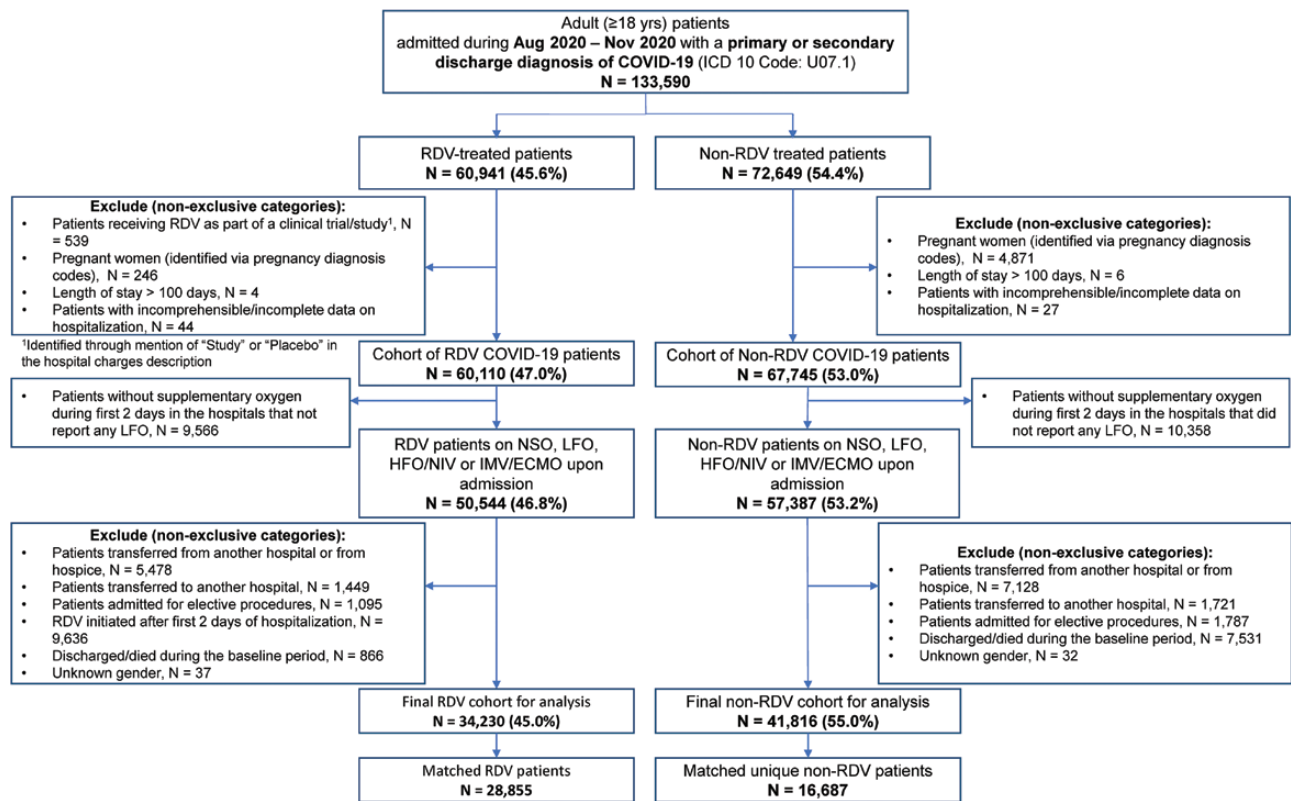
Figure 1. Study population.

To account for differences in hospital COVID-19 management practices, a preferential within-hospital matching approach with replacement was used:

1. Patients receiving RDV were matched to non-RDV patients with same baseline severity in 2-month blocks of admission (August–September, October–November) in the same hospital.
2. Unmatched patients in the RDV group were matched to non-RDV patients with same baseline severity in 2-month blocks of admission (August–September, October–November) in another RDV-using hospital of same bed-size category.

In addition, up to 1:10 variable matching ratio was allowed (ie, each RDV patient could be matched to at least 1 and at most 10 non-RDV patients) and the minimum difference between the PS of patients from the 2 groups (ie, caliper distance) was defined as 0.2 times the standard deviation of the logit of the PS. The matching with replacement approach allowed for most RDV patients to be matched despite the restrictive matching criteria. In addition, because there is likely to be considerable unmeasured confounding relating to the choice of treating perceived mild cases upon hospital admission, all patients included in the analysis were required to have at least 3 days of hospital stay from the time of index. This emulates previous study design approaches, including the ACTT-1 study [8, 23].

Mortality at 14 and 28 days was assessed using Kaplan-Meier curves and compared using log-rank tests. Cox proportional hazards models were used to derive hazard ratios (HR) and 95% CI. Models were adjusted for hospital-level cluster effects and the following covariates: age at admission, admission month, treatment at baseline (anticoagulants, convalescent plasma, corticosteroids, tocilizumab), hospital ward upon admission, and any baseline covariate with an absolute standardized difference of >0.15 in subgroups of patients receiving NSO, LFO, HFO/NIV, and IMV/ECMO.

Sensitivity Analyses

To examine the impact of hospital-level effects, these effects were removed from all steps of the analyses as follows: (1) hospital characteristics were excluded from PS calculation; (2) preferential within-hospital matching approach was not used; and (3) Cox proportional hazards models did not include hospital-level cluster effects. We also considered a stringent matching criterion (1:1 preferential within-hospital matching without replacement with same baseline severity and admission month). To assess the impact of statistical modeling approach, consistent with a number of other previous studies, logistic regression models with hospital-level random effects were also used to assess 14- and 28-day mortality. Finally, to assess the impact of requiring patients to remain in the hospital for at least 3 days

following index, and to reflect the lack of timestamps for treatment initiation, a sensitivity analysis was performed whereby patients were required to remain in the hospital for only 2 days following index.

RESULTS

Patient Population and Matching

After applying the inclusion and exclusion criteria, there were 34 230 patients in the RDV cohort and 41 816 patients in the non-RDV cohort. Before matching, patients receiving RDV had a mean age (standard deviation) of 64.2 (15.0) years of age, and the plurality were white with Medicare as primary payor, with a slight skew toward males (Table 1). Following matching, 28 855 patients receiving RDV were matched to 16 687 unique patients not receiving RDV (28 855 weighted because of matching with replacement with up to 1:10 variable ratio matching) (Figure 1). Most covariates had a standardized difference absolute value of <0.10 after matching, except primary payor (0.11), cardiovascular disease (0.11), renal disease (0.16), and age group (0.17) (Table 1).

Overall Cohort

Overall, 3057 (10.6%) and 4441 (15.4%) patients who received RDV died within 14 and 28 days, respectively, whereas 4437 (15.4%) and 5499 (19.1%) patients who did not receive RDV died within 14 and 28 days, respectively. Kaplan-Meier curves revealed a significantly lower risk of mortality in RDV vs non-RDV group ($P < .0001$) (Figure 2A). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV treated patients compared with non-RDV group (14-day adjusted HR [aHR]: 0.76; 95% CI: 0.69–0.83; 28-day aHR, 0.88; 95% CI: 0.81–0.96) (Figure 3).

Patients Requiring NSO (ie, Without Charges for Supplemental Oxygen) at Baseline

Among those on NSO, 427 (5.4%) and 635 (8.0%) patients who received RDV died within 14 and 28 days, respectively, whereas 726 (9.1%) and 916 (11.5%) patients who did not receive RDV died within 14 and 28 days, respectively. Kaplan-Meier curves revealed a significantly lower risk of mortality in RDV vs non-RDV group ($P < .0001$) (Figure 2B). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV-treated patients compared with non-RDV group (14-day aHR: 0.69; 95% CI: 0.57–0.83; 28-day aHR: 0.80; 95% CI: 0.68–0.94) (Figure 3).

Patients Requiring LFO at Baseline

Among those requiring LFO, 1028 (7.4%) and 1478 (10.7%) patients who received RDV died within 14 and 28 days, respectively, whereas 1661 (12.0%) and 2078 (15.1%) patients who did not receive RDV died within 14 and 28 days, respectively.

Kaplan-Meier curves revealed a significantly lower risk of mortality in RDV vs non-RDV group ($P < .0001$) (Figure 2C). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV-treated patients compared with the non-RDV group (14-day aHR: 0.67; 95% CI: 0.59–0.77; 28-day aHR: 0.76; 95% CI: 0.68–0.86) (Figure 3).

Patients Requiring HFO/NIV at Baseline

Among those requiring HFO/NIV, 1184 (20.5%) and 1701 (29.4%) patients who received RDV died within 14 and 28 days, respectively, whereas 1483 (25.7%) and 1782 (30.8%) patients who did not receive RDV died within 14 and 28 days, respectively. According to the log-rank test, there was no significant difference in risk of mortality between RDV and non-RDV groups at 28 days ($P = .1859$) (Figure 2D). After adjusting for baseline and clinical covariates, patients receiving RDV had a significantly lower risk of mortality at day 14 (aHR: 0.81; 95% CI: 0.70–0.93) compared with the non-RDV group, but there was no significant difference between the 2 groups at 28 days (aHR: 0.97; 95% CI: 0.84–1.11) (Figure 3).

Patients Requiring IMV/ECMO at Baseline

Among those requiring IMV/ECMO, 418 (32.3%) and 627 (48.4%) patients who received RDV died within 14 and 28 days, respectively, whereas 568 (43.8%) and 724 (55.8%) patients who did not receive RDV died within 14 and 28 days, respectively. Kaplan-Meier curves revealed a significantly lower risk of mortality in the RDV vs non-RDV group ($P < .0001$) (Figure 2E). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV-treated patients compared with the non-RDV group (14-day aHR: 0.70; 95% CI: 0.58–0.84; 28-day aHR: 0.81; 95% CI: 0.69–0.94) (Figure 3).

Sensitivity Analyses

The direction and magnitude of the study findings were consistent across sensitivity analyses of removing hospital-level effects and modifying the hospital stay requirement (Supplementary Tables 2 and 4). A stringent matching criterion (1:1 preferential-within hospital matching without replacement with same baseline severity and admission month) did not change the significances of the findings overall and in any of the subgroups. There was a single disparate finding using logistic regression models to examine 28-day mortality among patients on HFO (Supplementary Table 3). In this analysis, the adjusted OR was >1 for 28-day mortality (aOR: 1.10; 95% CI: 0.99–1.22), whereas the Cox proportional hazards model showed an adjusted HR of <1 (aHR: 0.97; 95% CI: 0.84–1.11). Neither of these differences were statistically significant.

Table 1. Demographic and Hospital Characteristics of Patients Hospitalized for COVID-19, August–November 2020

		All patients in Propensity Score Model			Propensity Score-matched Patients		
		No RDV	RDV	SMD	No RDV	RDV	SMD
		n = 41 816	n = 34 230		n = 28 855	n = 28 855	
Age group, y	18–34	2432 (5.8%)	1300 (3.8%)	0.28	693.7 (2.4%)	1022.0 (3.5%)	0.17
	35–49	5059 (12.1%)	4531 (13.2%)		3190.9 (11.1%)	3727.0 (12.9%)	
	50–64	10 222 (24.4%)	10 541 (30.8%)		8261.4 (28.6%)	8806.0 (30.5%)	
	65–74	9326 (22.3%)	8494 (24.8%)		7514.3 (26.0%)	7300.0 (25.3%)	
	75–84	8947 (21.4%)	6558 (19.2%)		6265.5 (21.7%)	5617.0 (19.5%)	
	85+	5830 (13.9%)	2806 (8.2%)		2929.1 (10.2%)	2383.0 (8.3%)	
Sex	Female	20 758 (49.6%)	15 126 (44.2%)	0.11	12 944.5 (44.9%)	12 820.0 (44.4%)	0.01
Race	White	28 259 (67.6%)	25 070 (73.2%)	0.19	21 209.7 (73.5%)	21 017.0 (72.8%)	0.03
	Black	8342 (19.9%)	4284 (12.5%)		3654.7 (12.7%)	3682.0 (12.8%)	
	Other	5215 (12.5%)	4876 (14.2%)		3990.5 (13.8%)	4156.0 (14.4%)	
Ethnicity	Hispanic	5761 (13.8%)	5501 (16.1%)	0.06	4482.7 (15.5%)	4787.0 (16.6%)	0.05
	Non-Hispanic	30 859 (73.8%)	24 971 (73.0%)		21 409.5 (74.2%)	20 888.0 (72.4%)	
	Unknown	5196 (12.4%)	3758 (11.0%)		2962.8 (10.3%)	3180.0 (11.0%)	
Primary payor	Commercial	8325 (19.9%)	10 160 (29.7%)	0.25	7330.9 (25.4%)	8379.0 (29.0%)	0.11
	Medicare	25 374 (60.7%)	18 020 (52.6%)		17 051.5 (59.1%)	15 447.0 (53.5%)	
	Medicaid	4483 (10.7%)	2784 (8.1%)		2158.5 (7.5%)	2345.0 (8.1%)	
	Other	3634 (8.7%)	3266 (9.5%)		2314.1 (8.0%)	2684.0 (9.3%)	
Admission month	August	11 377 (27.2%)	5265 (15.4%)	0.34	4860.7 (16.8%)	4634.0 (16.1%)	0.03
	September	6819 (16.3%)	4539 (13.3%)		3662.3 (12.7%)	3889.0 (13.5%)	
	October	9281 (22.2%)	8889 (26.0%)		7640.8 (26.5%)	7604.0 (26.4%)	
	November	14 339 (34.3%)	15 537 (45.4%)		12 691.2 (44.0%)	12 728.0 (44.1%)	
Admission source	Skilled nursing facility	1628 (3.9%)	684 (2.0%)	0.11	708.5 (2.5%)	604.0 (2.1%)	0.02
Bed size	0–199	7279 (17.4%)	7239 (21.1%)	0.10	5881.0 (20.4%)	5881.0 (20.4%)	0.00
	200–499	21 878 (52.3%)	16 987 (49.6%)		14 492.0 (50.2%)	14 492.0 (50.2%)	
	500+	12 659 (30.3%)	10 004 (29.2%)		8482.0 (29.4%)	8482.0 (29.4%)	
Rural/urban	Rural	5940 (14.2%)	5815 (17.0%)	0.08	4378.0 (15.2%)	4512.0 (15.6%)	0.01
	Urban	35 876 (85.8%)	28 415 (83.0%)		24 477.0 (84.8%)	24 343.0 (84.4%)	
Teaching	Yes	18 637 (44.6%)	14 633 (42.7%)	0.04	12 486.7 (43.3%)	12 292.0 (42.6%)	0.01
Region	Midwest	11 136 (26.6%)	10 686 (31.2%)	0.16	9357.7 (32.4%)	8592.0 (29.8%)	0.06
	Northeast	3229 (7.7%)	2047 (6.0%)		1642.7 (5.7%)	1707.0 (5.9%)	
	South	23 419 (56.0%)	17 485 (51.1%)		14 540.6 (50.4%)	15 153.0 (52.5%)	
	West	4032 (9.6%)	4012 (11.7%)		3314.0 (11.5%)	3403.0 (11.8%)	
Baseline comorbidities	Obesity	11 605 (27.8%)	13 697 (40.0%)	0.26	11 410.3 (39.5%)	11 782.0 (40.8%)	0.03
	COPD	9974 (23.9%)	9177 (26.8%)	0.07	8449.5 (29.3%)	7859.0 (27.2%)	0.05
	Cardiovascular disease (including hypertension)	34 248 (81.9%)	26 773 (78.2%)	0.09	24 046.2 (83.3%)	22 825.0 (79.1%)	0.11
	Diabetes	17 865 (42.7%)	14 440 (42.2%)	0.01	12 807.9 (44.4%)	12 381.0 (42.9%)	0.03
	Renal disease	12 555 (30.0%)	5791 (16.9%)	0.31	6817.5 (23.6%)	4970.0 (17.2%)	0.16
	Cancer	1883 (4.5%)	1293 (3.8%)	0.04	1178.1 (4.1%)	1094.0 (3.8%)	0.01
	Immunosuppressive condition	712 (1.7%)	1361 (4.0%)	0.14	1263.0 (4.4%)	1181.0 (4.1%)	0.01
Baseline hospital ward	General ward	33 476 (80.1%)	25 566 (74.7%)	0.12	20 191.7 (70.0%)	21 148.0 (73.3%)	0.07
	Stepdown	2518 (6.0%)	2226 (6.5%)		1864.4 (6.5%)	1872.0 (6.5%)	
	ICU	5822 (13.9%)	6438 (18.8%)		6798.9 (23.6%)	5835.0 (20.2%)	
Baseline severity	IMV/ECMO	1574 (3.8%)	1439 (4.2%)	0.63	1296.0 (4.5%)	1296.0 (4.5%)	0.00
	HFO/NIV	3179 (7.6%)	6365 (18.6%)		5781.0 (20.0%)	5781.0 (20.0%)	
	LFO	12 461 (29.8%)	16 415 (48.0%)		13 808.0 (47.9%)	13 808.0 (47.9%)	
	NSO	24 602 (58.8%)	10 011 (29.2%)		7970.0 (27.6%)	7970.0 (27.6%)	
Admitting diagnosis	Sepsis	2375 (5.7%)	2307 (6.7%)	0.04	2075.2 (7.2%)	2043.0 (7.1%)	0.00
	Respiratory failure	669 (1.6%)	849 (2.5%)	0.06	906.7 (3.1%)	736.0 (2.6%)	0.04
	Hypoxemia	393 (0.9%)	627 (1.8%)	0.08	429.6 (1.5%)	515.0 (1.8%)	0.02
	Pneumonia	993 (2.4%)	766 (2.2%)	0.01	615.8 (2.1%)	647.0 (2.2%)	0.01
Baseline medication use	Anticoagulants	8971 (21.5%)	4978 (14.5%)	0.18	4718.3 (16.4%)	4280.0 (14.8%)	0.04
	Corticosteroids	25 076 (60.0%)	32 795 (95.8%)	0.96	27 933.4 (96.8%)	27 692.0 (96.0%)	0.04
	Convalescent plasma	2645 (6.3%)	10 643 (31.1%)	0.67	9598.9 (33.3%)	9088.0 (31.5%)	0.04

Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; HFO/NIV, high-flow oxygen/noninvasive ventilation; ICU, intensive care unit; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation; LFO, low-flow oxygen; NSO, no supplemental oxygen charges; RDV, remdesivir; SMD, standardized mean difference.
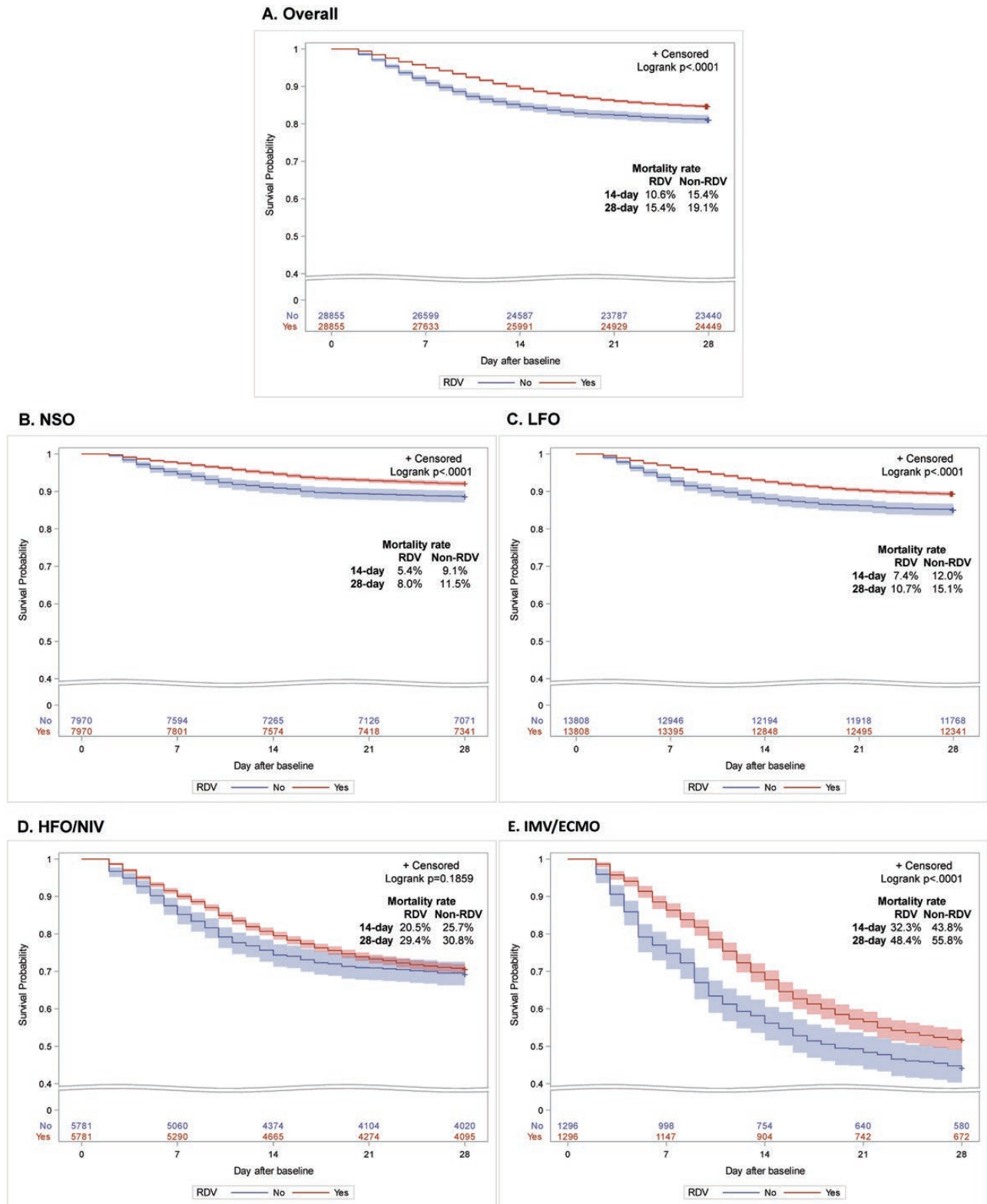
Figure 2. Kaplan-Meier curves among matched patients (preferential within-hospital matching) hospitalized for COVID-19, August–November 2020. *P* value from log-rank tests and mortality rates in the 2 treatments groups are presented for *A*, overall; *B*, no supplemental oxygen charges (NSO); *C*, low-flow oxygen (LFO); *D*, high-flow oxygen/non-invasive ventilation (HFO/NIV); and *E*, invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO). COVID-19, coronavirus disease 2019.
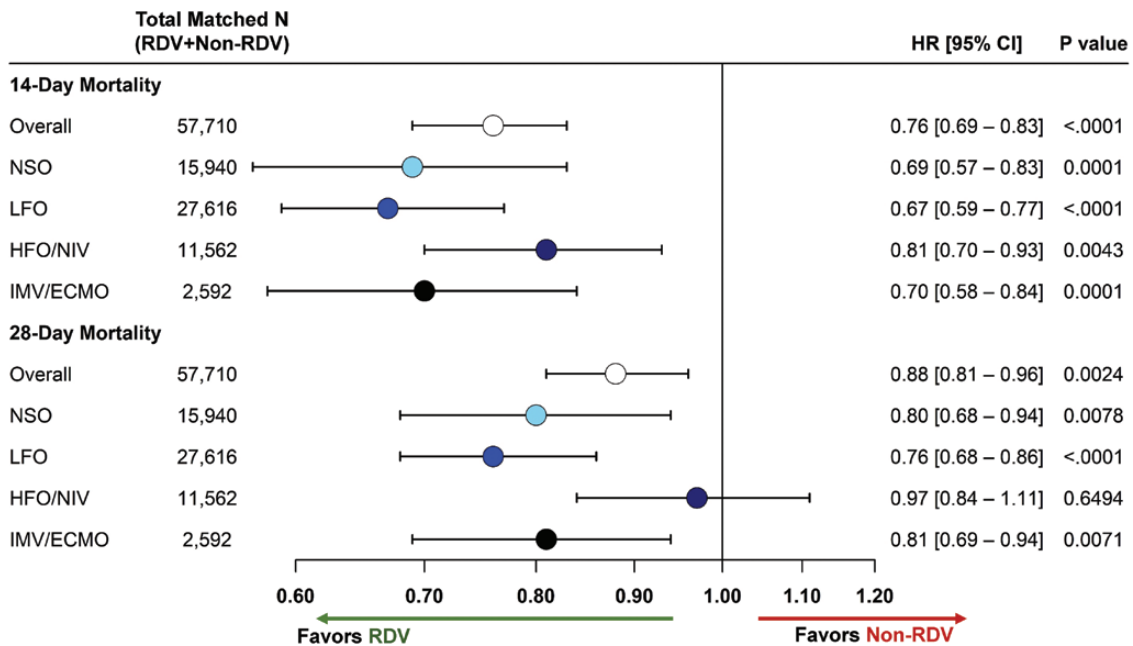
Figure 3. Cox proportional hazard model for time to 14- and 28-day mortality among matched patients (preferential within-hospital matching) hospitalized for COVID-19, August–November 2020. Adjusted for hospital-level random effects and age, admission month, anticoagulants use at baseline, convalescent plasma at baseline, corticosteroids use at baseline, tocilizumab use at baseline, intensive care unit stay/stepdown/general ward at baseline and other covariates with absolute standardized mean difference > 0.15. COVID-19, coronavirus disease 2019.

DISCUSSION

In this large, retrospective comparative effectiveness study of more than 100 000 patients, RDV initiation within the first 2 days of COVID-19 hospitalization was associated with improved survival compared with the non-RDV group. The beneficial effects of RDV at 14- and 28-day timepoints were most prominent among patients with NSO, LFO, or IMV/ECMO at baseline. A benefit at 14 days among patients requiring HFO was also observed. All findings were consistent across multiple sensitivity analyses. This study provides a robust analysis using contemporary data reflecting current treatment practices.

These data reinforce the findings from the double-blind, randomized, placebo-controlled ACTT-1 study and complement other observational studies supporting the clinical benefit of RDV in hastening clinical recovery and reducing mortality [8]. In ACTT-1, although RDV was not significantly associated with a decreased risk of mortality at day-29 in the overall group of patients, there was a significant mortality reduction associated with RDV treatment at day 15 (HR: 0.55; 95% CI: 0.36–0.83) in the overall group of patients and at 15 days (HR: 0.28; 95% CI: 0.12–0.66) and 29 days (HR: 0.30; 95% CI: 0.14–0.64) among patients requiring LFO. The magnitude of the effect shown in our study is smaller than observed in the trial, a possible reflection of the heterogeneous study population, the earlier study period of ACTT-1 when standard-of-care in the placebo arm may have been less evolved than standard-of-care in the non-RDV group in this study, and the high likelihood that residual

unmeasured confounding remains in our comparator group. Similarly, in the Solidarity trial, a trend toward mortality benefit was identified in nonventilated patients but did not reach significance using a 99% CI [14]; it is further noteworthy that 99% confidence intervals are stricter than typically applied for an objective clinical endpoint such as mortality. Recent meta-analyses of clinical trials showed mortality benefits in some of the patients such as those receiving some supplemental oxygen at baseline but not IMV/ECMO [17].

A comparative effectiveness study conducted between March and August 2020 found that RDV was associated with significantly improved time to recovery [24]. Although this study also found lower 28-day mortality, the time-to-mortality analysis was not significant (aHR: 0.70; 95% CI: 0.38–1.38). Given the substantially smaller sample of patients in the RDV group (N = 342) and low baseline mortality rate, this study may have been underpowered to detect a significant difference in mortality. A study conducted using data from a phase 3, randomized trial of RDV and an observational, retrospective cohort study found that RDV use was associated with a 62% reduction in mortality at 14 days (odds ratio: 0.38; 95% CI: 0.20–0.68) compared with standard of care [19]. A propensity-matched comparison with a larger non-RDV cohort also demonstrated survival advantage for RDV at 28 days [20]. RDV has also been demonstrated to have a favorable safety profile among patients with COVID-19 [28]. Among patients requiring HFO at baseline, RDV use was associated with reduced risk of mortality at

14 days but not at 28 days. Explanations for the lack of effectiveness of RDV at reducing mortality in this group of patients at 28 days are uncertain. A potential explanation may be due to a heterogeneous group consisting of patients who derive immediate benefit from RDV and survive and another group who derive a temporizing benefit from RDV to enable them to survive longer but nevertheless succumb at a later stage.

Strengths of this study include the use of a large administrative database of COVID-19 hospitalizations occurring across the United States. Additionally, robust matching methodology with a PS derived from comprehensive list of demographics, comorbidities, treatments (such as corticosteroids), and hospital-level characteristics in a large geographically diverse patient population was used. This study also included more contemporary data and excludes the early months of the pandemic, during which time limited understanding of the disease and overwhelmed hospital systems may have contributed to high patient mortality.

There are limitations to this study. As with all nonrandomized studies, residual confounding, unmeasured variables, and imbalances between groups can persist even after PS matching. To minimize these effects, we used a large sample size, rich administrative data, and adjustments for hospital-level differences in COVID-19 treatment practices. The database does not capture physicians' subjective impressions of patients' health status, which may have governed the decision to treat or not treat with RDV, potentially creating bias. Another limitation includes the potential for misclassification of some variables because variables based on billing and International Classification of Diseases, 10th revision, coding may misclassify or underrepresent comorbid conditions, treatments, and procedures. With administrative data, there is also a lack of confirmatory testing and imaging findings, necessitating the use of proxy measures of disease severity, such as evidence of oxygen use at baseline. Finally, bias may have been introduced with the exclusion criteria applied. Excluding patients who transferred out to other hospitals may have led to the selection of a healthier population if these patients had more severe disease, thereby affecting the generalizability of these findings.

In summary, in this retrospective comparative effectiveness study of more than 100 000 adults hospitalized with COVID-19 in the United States, treatment initiation with RDV upon hospital admission was associated with significant survival benefits at 14 and 28 days. These benefits were most apparent among patients receiving NSO, LFO, or IMV/ECMO at baseline. Although unmeasured confounding cannot be excluded, these findings provide further support that RDV antiviral therapy is a foundational treatment approach for COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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