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MAJOR ARTICLE

Remdesivir Is Associated With Reduced Mortality in COVID-19 Patients Requiring Supplemental Oxygen Including Invasive Mechanical Ventilation Across SARS-CoV-2 Variants

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Background. This comparative effectiveness study investigated the effect of remdesivir on in-hospital mortality among patients hospitalized for coronavirus disease 2019 (COVID-19) requiring supplemental oxygen including low-flow oxygen (LFO), high-flow oxygen/noninvasive ventilation (HFO/NIV), or invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) across variant of concern (VOC) periods.

Methods. Patients hospitalized for COVID-19 between December 2020 and April 2022 and administered remdesivir upon admission were 1:1 propensity score matched to patients not administered remdesivir during their COVID-19 hospitalization. Analyses were stratified by supplemental oxygen requirement upon admission and VOC period. Cox proportional hazards models were used to derive adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for 14- and 28-day mortality.

Results. Patients treated with remdesivir (67 582 LFO, 34 857 HFO/NIV, and 4164 IMV/ECMO) were matched to non-remdesivir patients. Unadjusted mortality rates were significantly lower for remdesivir-treated patients at 14 days (LFO: 6.4% vs. 8.8%; HFO/NIV: 16.8% vs. 19.4%; IMV/ECMO: 27.8% vs. 35.3%) and 28 days (LFO: 9.8% vs. 12.3%; HFO/NIV: 25.8% vs. 28.3%; IMV/ECMO: 41.4% vs. 50.6%). After adjustment, remdesivir treatment was associated with a statistically significant reduction in in-hospital mortality at 14 days (LFO: aHR, 0.72; 95% CI, 0.66–0.79; HFO/NIV: aHR, 0.83; 95% CI, 0.77–0.89; IMV/ECMO: aHR, 0.73; 95% CI, 0.65–0.82) and 28 days (LFO: aHR, 0.79; 95% CI, 0.73–0.85; HFO/NIV: aHR, 0.88; 95% CI, 0.82–0.93; IMV/ECMO: aHR, 0.74; 95% CI, 0.67–0.82) compared with non-remdesivir treatment. Lower risk of mortality among remdesivir-treated patients was observed across VOC periods.

Conclusions. Remdesivir treatment is associated with significantly reduced mortality among patients hospitalized for COVID-19 requiring supplemental oxygen upon admission, including those requiring HFO/NIV or IMV/ECMO with severe or critical disease, across VOC periods.

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

Despite improvements in standard of care, mortality rates in patients hospitalized for coronavirus disease 2019 (COVID-19) have remained high across variant of concern (VOC) periods. In the United States (US), ~1 in 2 patients with COVID-19 requiring invasive ventilation died since the beginning of the pandemic [1–3]. It remains essential to continue to evaluate therapeutic options to treat patients throughout the spectrum of COVID-19 disease and VOC periods.

Remdesivir has maintained effective antiviral activity against all clinically relevant VOC and retains an important role in the management of COVID-19 [4]. Based on the findings from randomized controlled trials such as the Adaptive COVID-19 Treatment Trial (ACTT-1) and the SOLIDARITY trial, which demonstrated that remdesivir improved time to recovery and reduced mortality in hospitalized patients [5, 6], most clinical guidelines recommend initiation of remdesivir among patients requiring low-flow oxygen (LFO) [7, 8]. In addition, current

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World Health Organization (WHO) guidelines include a conditional recommendation for the use of remdesivir in patients with severe disease, defined by the WHO as oxygen saturation <90% measured by pulse oximetry, signs of pneumonia, or signs of respiratory distress [5]. However, there is no such recommendation in critically ill patients, defined by the WHO as patients with acute respiratory distress syndrome, sepsis, septic shock and/or multiple organ dysfunction and/or requiring noninvasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). This lack of recommendation for remdesivir use in critically ill patients may reflect either lower efficacy or, alternatively, the inability to detect beneficial effects, as clinical trials were not designed or powered to detect differences in remdesivir efficacy in subgroups according to baseline COVID-19 severity. In contrast, data from real-world studies have indicated a potential beneficial role for remdesivir in critically ill patients in whom the hyperinflammatory response has already developed [9–11].

Given the conflicting findings, the emergence of new VOC, and the ongoing need for effective therapeutics, it is paramount to further examine the role of remdesivir in the treatment of patients requiring supplemental oxygen to inform clinical guidelines. Therefore, the aim of the present study was to evaluate clinical practice experiences and compare 14- and 28-day mortality in remdesivir-treated vs. non-remdesivir patients hospitalized for COVID-19 who required supplemental oxygen (LFO, HFO/NIV, or IMV/ECMO) upon admission across VOC periods: pre-Delta, Delta-predominant, and Omicron-predominant (pre-BA4/5 period).

METHODS

Study Design and Data Source

Data for this retrospective comparative effectiveness study were extracted from the US PINC AI Healthcare Database, which is a large, geographically diverse, all-payer hospital administrative database that captures diagnosis, procedure, and medication data for ~25% of all hospitalizations occurring in the US. This database is a visit-level chargemaster/billing database wherein a patient record begins on the first day of the inpatient encounter and clinical practice activities at the day level are available until the day of discharge. Actual dates and times are not available in the database due to privacy concerns, so all data are captured relative to the hospital admission day.

Study Population

Patients aged ≥18 years who were hospitalized for COVID-19 between December 1, 2020, and April 30, 2022 and required supplemental oxygen upon admission, defined as the first 2 days of hospitalization, were included. COVID-19 admissions were identified by the presence of a primary discharge diagnosis of COVID-19, defined as an International Classification of Diseases, 10th revision, Clinical Modification code of U07.1 that was also flagged as "present on admission." Supplemental oxygenation requirement upon admission was determined by the presence of relevant billing charges for LFO, HFO/NIV, and IMV/ECMO. A prespecified study protocol and analysis plan outlined separate assessment of patients with different levels of supplemental oxygen requirements upon admission.

For patients with multiple COVID-19 admissions during the study period, only the first admission for COVID-19 was included in the analyses. Patients were excluded from the study population if they met any of the following criteria: pregnancy, incomplete data, died or were discharged within 2 days of admission, transferred from hospice, transferred to or from another hospital, admitted for an elective procedure, or initiated remdesivir after the first 2 days of hospitalization.

Remdesivir-treated patients were administered at least a single dose of remdesivir within 2 days of hospitalization for COVID-19, while non-remdesivir patients did not receive remdesivir at any time during their hospitalization. Patients crossing over to initiate remdesivir later (ie, after the first 2 days of hospitalization) were excluded given the prespecified research objective to examine patients with a primary diagnosis of COVID-19 present on admission and to compare outcomes among those receiving prompt antiviral therapy vs. those not receiving it. In addition, patients who initiated antiviral therapy at a later time point of their admission were likely to have had confounding reasons, and thus identifying a corresponding clinical match was not feasible.

Main Outcome and Covariates

Baseline was defined as the first 2 days of hospitalization. This definition was chosen as actual dates and time stamps are unavailable in the database, such that for a patient admitted to hospital at 23:59, that patient's day 2 would start at 00:00. The definition for baseline therefore provided all patients with a window of at least 24 hours in which clinical decisions were made and implemented.

The primary outcome of all-cause in-hospital mortality was assessed at 14 and 28 days after hospitalization for COVID-19. In-hospital mortality was defined as a discharge status of either "expired" or "hospice." Patients who were discharged alive or not into a hospice care setting were censored at 14 and 28 days, respectively.

The full list and definitions of baseline covariates are provided in the Supplementary Data.

Statistical Analysis

Analyses were conducted in groups stratified by supplemental oxygen requirement (LFO, HFO/NIV, or IMV/ECMO) and by VOC period (pre-Delta [December 2020 to April 2021], Delta-predominant [May 2021 to November 2021], and Omicron-predominant [December 2021 to April 2022, pre-BA4/5 period]). To account for potential indication bias

according to remdesivir administration, propensity score (PS) methods were used to balance patient characteristics. PS were estimated for each VOC period and for patients requiring LFO, HFO/NIV, and IMV/ECMO at baseline using separate logistic regression models. The models included the following patient and hospital characteristics: demographics (age group, gender, race, ethnicity, primary payor), comorbidity groups (obesity, chronic obstructive pulmonary disorder, cardiovascular disease, diabetes mellitus, renal disease, cancer, immunosuppressive conditions), hospital characteristics (hospital bed size, teaching, region, urban/rural), COVID-19 severity (hospital ward upon admission, admission diagnoses such as sepsis, respiratory failure, hypoxemia, and pneumonia), baseline concomitant COVID-19 treatments (anticoagulants, corticosteroids, convalescent plasma, baricitinib, tocilizumab), admission month, and admission source. All covariates were retained in the model irrespective of their *P* value.

To account for differences in hospital COVID-19 management practices that may have evolved with each VOC, a 1:1 preferential within-hospital matching approach with replacement with a caliper distance of 0.2 times the standard deviation of the logit of the PS was implemented as follows:

1. Patients receiving remdesivir were matched to non-remdesivir patients within the caliper distance and the same age group (18–49, 50–64, ≥65 years) in 2-to-3-month blocks of admission month within the VOC period within the same hospital.
2. The unmatched patients in the remdesivir group were then matched to non-remdesivir patients within the caliper distance and the same age group (18–49, 50–64, ≥65 years) in 2-to-3-month blocks of admission month within the VOC period from another remdesivir-using hospital of similar bed-size (0–199, 200–499, 500+ beds).

A 1:1 matching with replacement approach was undertaken to allow for most of the remdesivir patients to be matched and included in the analysis. There was no limit to the number of times a non-remdesivir patient was available for matching to a remdesivir patient. Weighted non-remdesivir numbers are presented. Further, all patients included in the analysis were required to have at least 3 days of hospital stay from administration of remdesivir. This emulates previous study design approaches [6, 9, 10]

Time to 14- and 28-day in-hospital mortality was assessed using Kaplan-Meier curves and compared using log-rank tests. Cox proportional hazards models were used to derive adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs), adjusted for hospital-level cluster effects, age, admission month, hospital ward upon admission (intensive care unit [ICU]/step-down unit vs. general ward), and baseline concomitant COVID-19 treatments. A robust (sandwich) variance estimator was used to account for potential replications of patients induced by the matching with replacement approach, which resulted in conservative (wider) 95% CIs.

RESULTS

Between December 2020 and April 2022, the database included 219 028 patients hospitalized for COVID-19 who required LFO, 108 171 patients hospitalized for COVID-19 who required HFO/NIV, and 45 269 patients hospitalized for COVID-19 who required IMV/ECMO at baseline (Figure 1).

LFO Patients

After applying the inclusion and exclusion criteria, there were 116 012 patients who required LFO upon admission, including 81 811 (70.5%) patients administered remdesivir within the first 2 days of hospitalization and 34 201 (29.5%) patients not administered remdesivir during hospitalization for COVID-19 (Figure 1).

Before matching, remdesivir-treated patients were younger than non-remdesivir patients (median age [interquartile range {IQR}], 63 [51–74] vs. 67 [56–78] years). Before matching, remdesivir-treated patients were also less likely to have renal disease than non-remdesivir patients (13.5% vs. 27.4%) (Table 1).

Following matching, the LFO cohort comprised 67 582 remdesivir-treated patients and 18 830 unique non-remdesivir patients, weighted to 67 582 patients following 1:1 matching with replacement. All covariates were well balanced between remdesivir-treated and non-remdesivir patients with an absolute standardized difference ≤0.10 (Table 1).

Across VOC periods, 4315 (6.4%) remdesivir-treated patients died within 14 days compared with 5918 (8.8%) matched non-remdesivir patients. By 28 days, 6641 (9.8%) remdesivir-treated and 8305 (12.3%) matched non-remdesivir patients had died. In the unadjusted analysis, risk of mortality was significantly lower in remdesivir-treated patients compared with non-remdesivir patients (log-rank test: $P < .0001$) (Figure 2). After adjustment for covariates, remdesivir initiation was associated with a significant reduction in in-hospital mortality compared with non-remdesivir use (14-day aHR, 0.72; 95% CI, 0.66–0.79; 28-day aHR, 0.79; 95% CI, 0.73–0.85) (Figure 3). The impact of early remdesivir initiation was consistent across VOC periods (Figure 3).

HFO/NIV Patients

After applying the inclusion and exclusion criteria, there were 54 529 patients who required HFO/NIV upon admission, including 39 034 (71.6%) patients administered remdesivir in the first 2 days of hospitalization and 15 495 (28.4%) patients not administered remdesivir during hospitalization for COVID-19 (Figure 1).

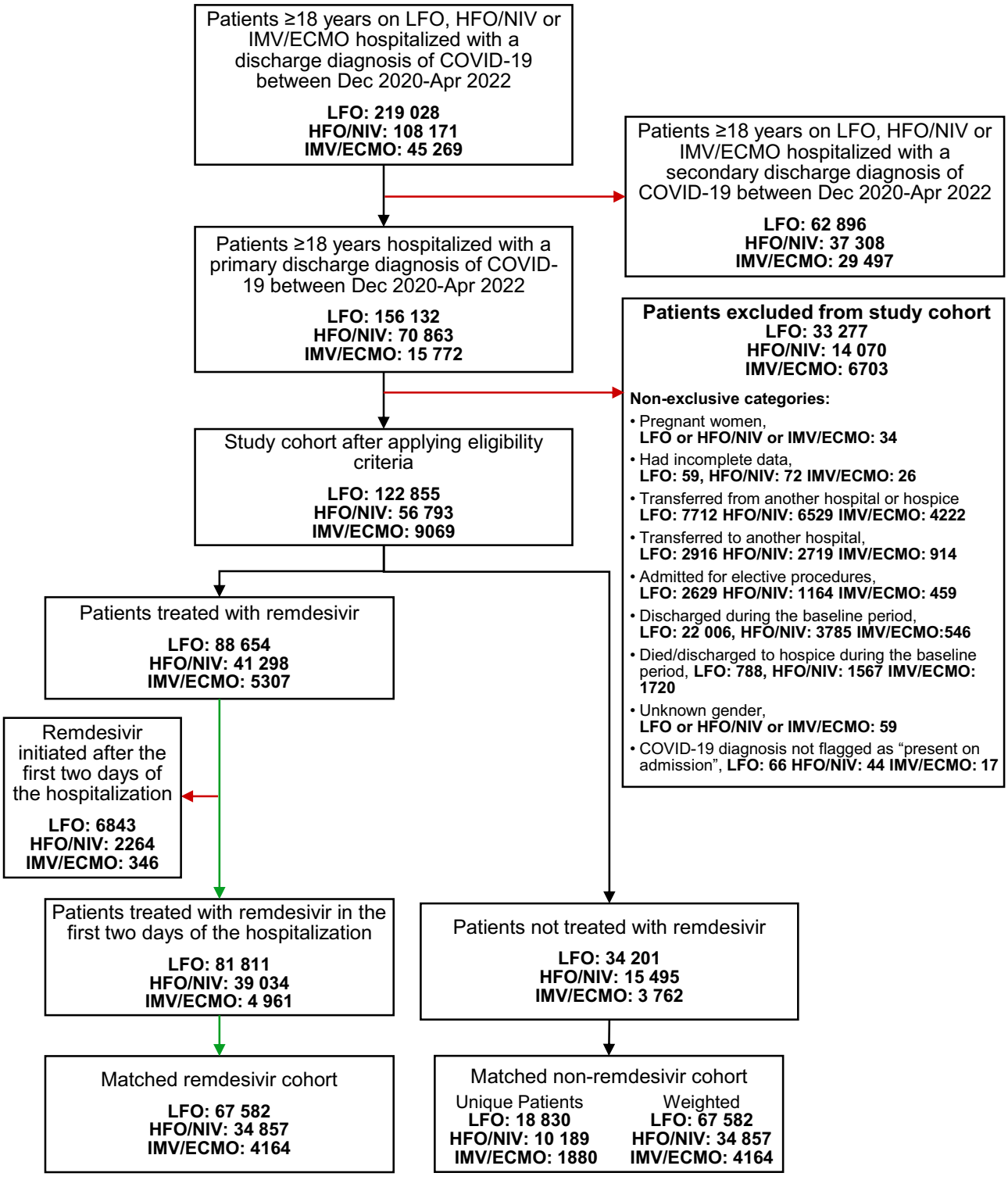

Figure 1. Study population. Abbreviations: HFO/NIV, high-flow oxygen/noninvasive ventilation; IMV/ECMO, invasive mechanical ventilation/membrane oxygenation; LFO, low-flow oxygen.

Before matching in the HFO/NIV cohort, a smaller proportion of remdesivir-treated patients were aged 65 years or older compared with non-remdesivir patients (45.5% vs. 52.1%). Before matching, remdesivir-treated patients were also less likely to have renal disease (17.5% vs. 31.6%) or be immunocompromised (24.8% vs. 38.2%) compared with non-remdesivir patients (Table 1).

Table 1. Demographic and Hospital Characteristics of Patients Hospitalized for COVID-19, Dec 2020–Apr 2022

LFO upon admission		Before Matching		After Matching[a]	
		Non-remdesivir n = 34 201	Remdesivir n = 81 811	Non-remdesivir (Weighted) n= 67 582	Remdesivir n = 67 582
Age group, y	18–49	5321 (15.6)	18 202 (22.2)	14 099 (20.9)	14 099 (20.9)
	50–64	9588 (28.0)	26 128 (31.9)	21 490 (31.8)	21 490 (31.8)
	65+	19 292 (56.4)	37 481 (45.8)	31 993 (47.3)	31 993 (47.3)
Gender	Female	17 320 (50.6)	39 824 (48.7)	32 208 (47.7)	32 965 (48.8)
Race	White	25 665 (75.0)	61 007 (74.6)	51 540 (76.3)	50 389 (74.6)
	Black	5033 (14.7)	10 006 (12.2)	7491 (11.1)	8212 (12.2)
	Asian	506 (1.5)	1651 (2.0)	1333 (2.0)	1397 (2.1)
	Other	2997 (8.8)	9147 (11.2)	7218 (10.7)	7584 (11.2)
Ethnicity	Hispanic	3642 (10.6)	13 093 (16.0)	9885 (14.6)	10 653 (15.8)
	Non-Hispanic	27 356 (80.0)	62 731 (76.7)	52 714 (78.0)	51 889 (76.8)
	Unknown	3203 (9.4)	5987 (7.3)	4983 (7.4)	5040 (7.5)
Primary payor	Commercial	8180 (23.9)	26 860 (32.8)	21 072 (31.2)	21 614 (32.0)
	Medicare	20 167 (59.0)	38 718 (47.3)	33 585 (49.7)	32 941 (48.7)
	Medicaid	2938 (8.6)	8250 (10.1)	6464 (9.6)	6516 (9.6)
	Other	2916 (8.5)	7983 (9.8)	6461 (9.6)	6511 (9.6)
Variant period	Pre-Delta	11 952 (34.9)	31 780 (38.8)	26 455 (39.2)	26 455 (39.2)
	Delta	12 391 (36.2)	34 788 (42.5)	28 819 (42.6)	28 819 (42.6)
	Omicron	9858 (28.8)	15 243 (18.6)	12 308 (18.2)	12 308 (18.2)
Admission source	Transfer from SNF or ICF	572 (1.7)	861 (1.1)	838 (1.2)	745 (1.1)
Hospital size, no. of beds	<100	2838 (8.3)	7183 (8.8)	5349 (7.9)	5734 (8.5)
	100–199	5853 (17.1)	18 478 (22.6)	15 437 (22.8)	15 052 (22.3)
	200–299	8058 (23.6)	17 712 (21.6)	14 772 (21.9)	14 810 (21.9)
	300–399	6817 (19.9)	13 715 (16.8)	11 143 (16.5)	11 670 (17.3)
	400–499	4088 (12.0)	7009 (8.6)	6322 (9.4)	5757 (8.5)
	500+	6547 (19.1)	17 714 (21.7)	14 559 (21.5)	14 559 (21.5)
Hospital location	Urban	28 921 (84.6)	67 110 (82.0)	56 384 (83.4)	55 838 (82.6)
	Rural	5280 (15.4)	14 701 (18.0)	11 198 (16.6)	11 744 (17.4)
Teaching hospital		12 738 (37.2)	27 058 (33.1)	21 893 (32.4)	22 528 (33.3)
Region	Midwest	8534 (25.0)	18 170 (22.2)	15 304 (22.6)	14 860 (22.0)
	Northeast	1488 (4.4)	4554 (5.6)	3720 (5.5)	3588 (5.3)
	South	19 459 (56.9)	47 936 (58.6)	38 935 (57.6)	39 885 (59.0)
	West	4720 (13.8)	11 151 (13.6)	9623 (14.2)	9249 (13.7)
Comorbidities	Obesity	11 096 (32.4)	31 473 (38.5)	25 841 (38.2)	26 104 (38.6)
	COPD	9713 (28.4)	21 696 (26.5)	18 465 (27.3)	18 062 (26.7)
	Cardiovascular disease	27 261 (79.7)	58 867 (72.0)	49 872 (73.8)	49 486 (73.2)
	Diabetes mellitus	13 473 (39.4)	29 245 (35.7)	24 667 (36.5)	24 608 (36.4)
	Renal disease	9357 (27.4)	11 044 (13.5)	10 058 (14.9)	9502 (14.1)
	Cancer	1398 (4.1)	2793 (3.4)	2528 (3.7)	2381 (3.5)
Immunocompromised condition		11 675 (34.1)	17 022 (20.8)	15 206 (22.5)	14 533 (21.5)
Hospital ward upon admission	General ward	29 703 (86.8)	69 809 (85.3)	57 850 (85.6)	57 686 (85.4)
	ICU/step-down	4498 (13.2)	12 002 (14.7)	9732 (14.4)	9896 (14.6)
Admit diagnosis	Sepsis	151 (0.4)	251 (0.3)	173 (0.3)	214 (0.3)
	Pneumonia/respiratory failure	2652 (7.8)	5114 (6.3)	3935 (5.8)	4185 (6.2)
Other COVID-19 treatments at baseline	Anticoagulants	9959 (29.1)	14 398 (17.6)	12 433 (18.4)	12 238 (18.1)
	Corticosteroids	30 695 (89.7)	79 947 (97.7)	66 256 (98.0)	66068 (97.8)
	Convalescent plasma	1081 (3.2)	8545 (10.4)	6216 (9.2)	6119 (9.1)
	Tocilizumab	1265 (3.7)	4205 (5.1)	3728 (5.5)	3659 (5.4)
	Baricitinib	2479 (7.2)	4635 (5.7)	3431 (5.1)	3992 (5.9)

Table 1. Continued

		Before Matching		After Matching[a]	
		Non-remdesivir n = 15 495	Remdesivir n = 39 034	Non-remdesivir (weighted) n = 34 857	Remdesivir n = 34 857
HFO/NIV upon admission					
Age group, y	18–49	2342 (15.1)	7745 (19.8)	6572 (18.9)	6572 (18.9)
	50–64	5080 (32.8)	13 542 (34.7)	12 206 (35.0)	12 206 (35.0)
	65+	8073 (52.1)	17 747 (45.5)	16 079 (46.1)	16 079 (46.1)
Gender	Female	6674 (43.1)	16 722 (42.8)	14 881 (42.7)	14 991 (43.0)
Race	White	11 527 (74.4)	28 635 (73.4)	25 753 (73.9)	25 638 (73.6)
	Black	2449 (15.8)	5567 (14.3)	4685 (13.4)	5005 (14.4)
	Asian	197 (1.3)	831 (2.1)	664 (1.9)	696 (2.0)
	Other	1322 (8.5)	4001 (10.3)	3755 (10.8)	3518 (10.1)
Ethnicity	Hispanic	1400 (9.0)	5697 (14.6)	4788 (13.7)	4825 (13.8)
	Non-Hispanic	12 771 (82.4)	29 559 (75.7)	26 694 (76.6)	26 633 (76.4)
	Unknown	1324 (8.5)	3778 (9.7)	3375 (9.7)	3399 (9.8)
Primary payor	Commercial	3794 (24.5)	12 160 (31.2)	10 935 (31.4)	10 791 (31.0)
	Medicare	8709 (56.2)	18 830 (48.2)	16 979 (48.7)	16 979 (48.7)
	Medicaid	1629 (10.5)	4627 (11.9)	4058 (11.6)	4062 (11.7)
	Other	1363 (8.8)	3417 (8.8)	2885 (8.3)	3025 (8.7)
Variant period	Pre-Delta	4279 (27.6)	13 661 (35.0)	12 160 (34.9)	12 160 (34.9)
	Delta	6050 (39.0)	16 914 (43.3)	15 166 (43.5)	15 166 (43.5)
	Omicron	5166 (33.3)	8459 (21.7)	7531 (21.6)	7531 (21.6)
Admission source	Transfer from SNF or ICF	283 (1.8)	547 (1.4)	475 (1.4)	480 (1.4)
Hospital size, no. of beds	<100	1343 (8.7)	3112 (8.0)	2914 (8.4)	2727 (7.8)
	100–199	2159 (13.9)	6687 (17.1)	5656 (16.2)	5843 (16.8)
	200–299	3031 (19.6)	8328 (21.3)	7558 (21.7)	7524 (21.6)
	300–399	3071 (19.8)	7189 (18.4)	6303 (18.1)	6581 (18.9)
	400–499	1866 (12.0)	4052 (10.4)	3963 (11.4)	3719 (10.7)
	500+	4025 (26.0)	9666 (24.8)	8463 (24.3)	8463 (24.3)
Hospital location	Urban	12 672 (81.8)	32 662 (83.7)	29 298 (84.1)	29 147 (83.6)
	Rural	2823 (18.2)	6372 (16.3)	5559 (15.9)	5710 (16.4)
Teaching hospital		7025 (45.3)	15 061 (38.6)	13 403 (38.5)	13 544 (38.9)
Region	Midwest	3563 (23.0)	7584 (19.4)	6889 (19.8)	6877 (19.7)
	Northeast	1368 (8.8)	4412 (11.3)	3832 (11.0)	3775 (10.8)
	South	8400 (54.2)	21 902 (56.1)	19 593 (56.2)	19 579 (56.2)
	West	2164 (14.0)	5136 (13.2)	4543 (13.0)	4626 (13.3)
Comorbidities	Obesity	7279 (47.0)	19 777 (50.7)	17 320 (49.7)	17 600 (50.5)
	COPD	5133 (33.1)	12 179 (31.2)	10 300 (29.5)	10 743 (30.8)
	Cardiovascular disease	13 332 (86.0)	31 984 (81.9)	28 679 (82.3)	28 693 (82.3)
	Diabetes mellitus	7059 (45.6)	17 230 (44.1)	15 143 (43.4)	15 370 (44.1)
	Renal disease	4902 (31.6)	6823 (17.5)	6210 (17.8)	6142 (17.6)
	Cancer	616 (4.0)	1290 (3.3)	1126 (3.2)	1146 (3.3)
Immunocompromised condition		5924 (38.2)	9690 (24.8)	8820 (25.3)	8714 (25.0)
Hospital ward upon admission	General ward	10 186 (65.7)	26 199 (67.1)	22 778 (65.3)	23 237 (66.7)
	ICU/step-down	5309 (34.3)	12 835 (32.9)	12 079 (34.7)	11 620 (33.3)
Admit diagnosis	Sepsis	84 (0.5)	151 (0.4)	145 (0.4)	136 (0.4)
	Pneumonia/respiratory failure	1261 (8.1)	2915 (7.5)	2673 (7.7)	2643 (7.6)
Other COVID-19 treatments at baseline	Anticoagulants	5010 (32.3)	8819 (22.6)	7980 (22.9)	7977 (22.9)
	Corticosteroids	14 197 (91.6)	38 192 (97.8)	34 224 (98.2)	34 186 (98.1)
	Convalescent plasma	434 (2.8)	3751 (9.6)	2686 (7.7)	2603 (7.5)
	Tocilizumab	1967 (12.7)	5775 (14.8)	5339 (15.3)	5199 (14.9)
	Baricitinib	2447 (15.8)	5475 (14.0)	5021 (14.4)	5110 (14.7)

Table 1. Continued

		Before Matching		After Matching[a]	
		Non-remdesivir n = 3762	Remdesivir n = 4961	Non-remdesivir (Weighted) n = 4164	Remdesivir n = 4164
IMV/ECMO upon admission					
Age group, y	18–49	819 (21.8)	1113 (22.4)	892 (21.4)	892 (21.4)
	50–64	1246 (33.1)	1751 (35.3)	1474 (35.4)	1474 (35.4)
	65+	1697 (45.1)	2097 (42.3)	1798 (43.2)	1798 (43.2)
Gender	Female	1632 (43.4)	2231 (45.0)	1876 (45.1)	1880 (45.1)
Race	White	2462 (65.4)	3382 (68.2)	2728 (65.5)	2841 (68.2)
	Black	751 (20.0)	848 (17.1)	802 (19.3)	715 (17.2)
	Asian	65 (1.7)	127 (2.6)	117 (2.8)	93 (2.2)
	Other	484 (12.9)	604 (12.2)	517 (12.4)	515 (12.4)
Ethnicity	Hispanic	527 (14.0)	755 (15.2)	586 (14.1)	628 (15.1)
	Non-Hispanic	2875 (76.4)	3717 (74.9)	3169 (76.1)	3125 (75.0)
	Unknown	360 (9.6)	489 (9.9)	409 (9.8)	411 (9.9)
Primary payor	Commercial	808 (21.5)	1295 (26.1)	1107 (26.6)	1044 (25.1)
	Medicare	1979 (52.6)	2355 (47.5)	1988 (47.7)	2018 (48.5)
	Medicaid	610 (16.2)	823 (16.6)	684 (16.4)	690 (16.6)
	Other	365 (9.7)	488 (9.8)	385 (9.2)	412 (9.9)
Variant period	Pre-Delta	1098 (29.2)	1742 (35.1)	1389 (33.4)	1389 (33.4)
	Delta	1453 (38.6)	2082 (42.0)	1765 (42.4)	1765 (42.4)
	Omicron	1211 (32.2)	1137 (22.9)	1010 (24.2)	1010 (24.2)
Admission source	Transfer from SNF or ICF	90 (2.4)	82 (1.7)	65 (1.6)	74 (1.8)
Hospital size, no. of beds	<100	109 (2.9)	244 (4.9)	159 (3.8)	181 (4.3)
	100–199	417 (11.1)	788 (15.9)	611 (14.7)	589 (14.1)
	200–299	689 (18.3)	1011 (20.4)	831 (20.0)	857 (20.6)
	300–399	793 (21.1)	952 (19.2)	865 (20.8)	807 (19.4)
	400–499	542 (14.4)	524 (10.6)	439 (10.5)	471 (11.3)
	500+	1212 (32.2)	1442 (29.1)	1259 (30.2)	1259 (30.2)
Hospital location	Urban	3383 (89.9)	4200 (84.7)	3566 (85.6)	3589 (86.2)
	Rural	379 (10.1)	761 (15.3)	598 (14.4)	575 (13.8)
Teaching hospital		1954 (51.9)	2255 (45.5)	1896 (45.5)	1959 (47.0)
Region	Midwest	831 (22.1)	923 (18.6)	765 (18.4)	789 (18.9)
	Northeast	345 (9.2)	473 (9.5)	427 (10.3)	408 (9.8)
	South	1959 (52.1)	2898 (58.4)	2385 (57.3)	2390 (57.4)
	West	627 (16.7)	667 (13.4)	587 (14.1)	577 (13.9)
Comorbidities	Obesity	1708 (45.4)	2679 (54.0)	2301 (55.3)	2219 (53.3)
	COPD	1175 (31.2)	1497 (30.2)	1321 (31.7)	1255 (30.1)
	Cardiovascular disease	3452 (91.8)	4383 (88.3)	3772 (90.6)	3725 (89.5)
	Diabetes mellitus	1892 (50.3)	2484 (50.1)	2118 (50.9)	2092 (50.2)
	Renal disease	1235 (32.8)	1021 (20.6)	994 (23.9)	897 (21.5)
	Cancer	127 (3.4)	158 (3.2)	136 (3.3)	136 (3.3)
Immunocompromised condition		1500 (39.9)	1321 (26.6)	1260 (30.3)	1173 (28.2)
Hospital ward upon admission	General ward	635 (16.9)	1150 (23.2)	856 (20.6)	899 (21.6)
	ICU/step-down	3127 (83.1)	3811 (76.8)	3308 (79.4)	3265 (78.4)
Admit diagnosis	Sepsis	51 (1.4)	46 (0.9)	33 (0.8)	38 (0.9)
	Pneumonia/respiratory failure	356 (9.5)	456 (9.2)	363 (8.7)	398 (9.6)
Other COVID-19 treatments at baseline	Anticoagulants	1700 (45.2)	1557 (31.4)	1402 (33.7)	1367 (32.8)
	Corticosteroids	3282 (87.2)	4770 (96.1)	4045 (97.1)	4016 (96.4)
	Convalescent plasma	115 (3.1)	501 (10.1)	296 (7.1)	294 (7.1)
	Tocilizumab	523 (13.9)	1045 (21.1)	904 (21.7)	800 (19.2)
	Baricitinib	405 (10.8)	674 (13.6)	500 (12.0)	562 (13.5)

Abbreviation: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICF, intermediate care facility; ICU, intensive care unit; LFO, low-flow oxygen; RDV, remdesivir; SNF, skilled nursing facility.

[a]Matching with replacement approach.

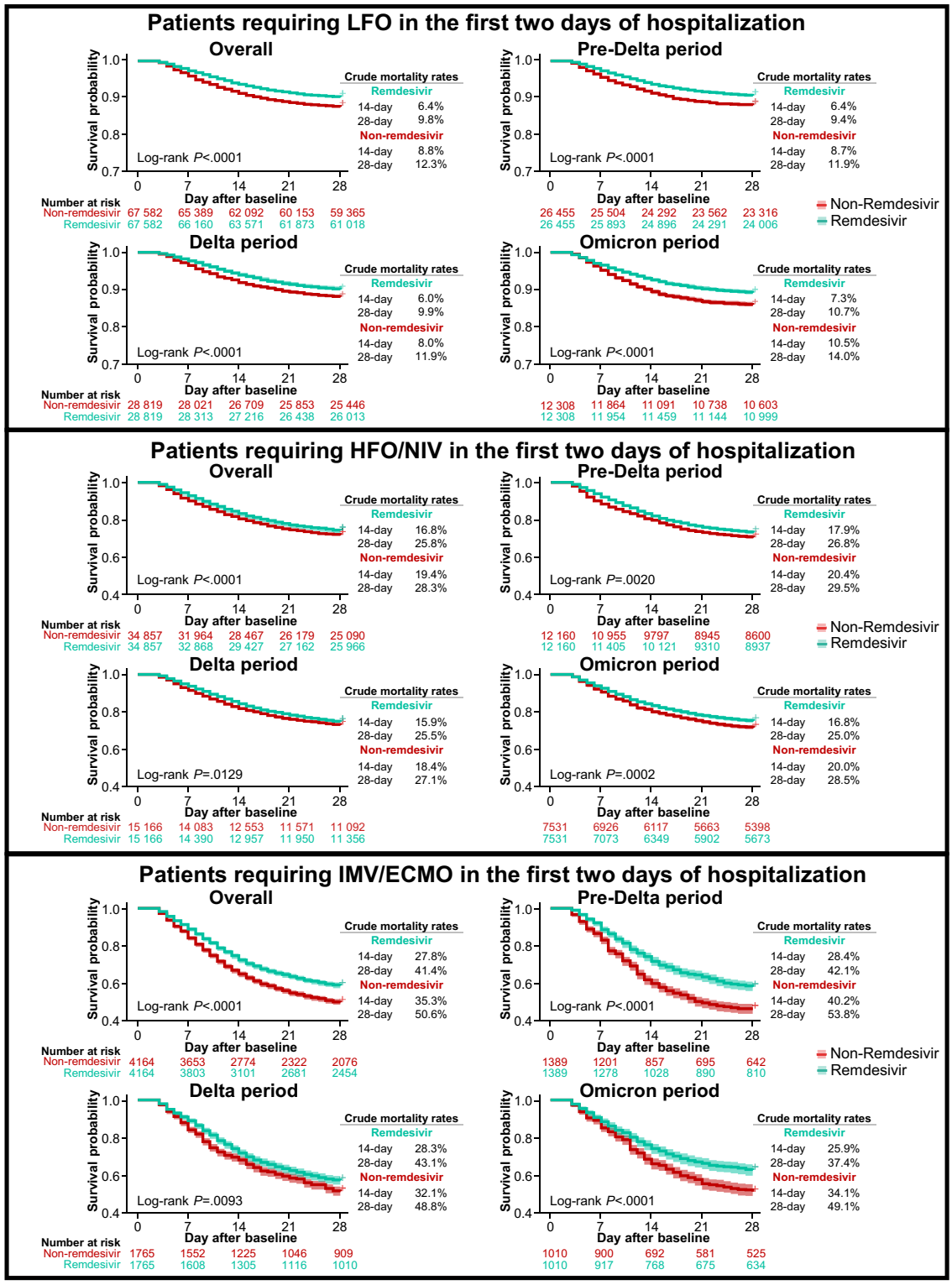

Figure 2. Kaplan-Meier curves for time to mortality among patients requiring LFO, HFO/NIV, and IMV/ECMO across the COVID-19 variant periods. The sample sizes for the non-remdesivir group are weighted since matching with replacement approach was used. Days after baseline refers to the time during which outcomes were assessed following the 2-day period in which remdesivir treatment administration was identified (baseline). Abbreviations: HFO/NIV, high-flow oxygen/noninvasive ventilation; IMV/ECMO, invasive mechanical ventilation/membrane oxygenation; LFO, low-flow oxygen; RDV, remdesivir.

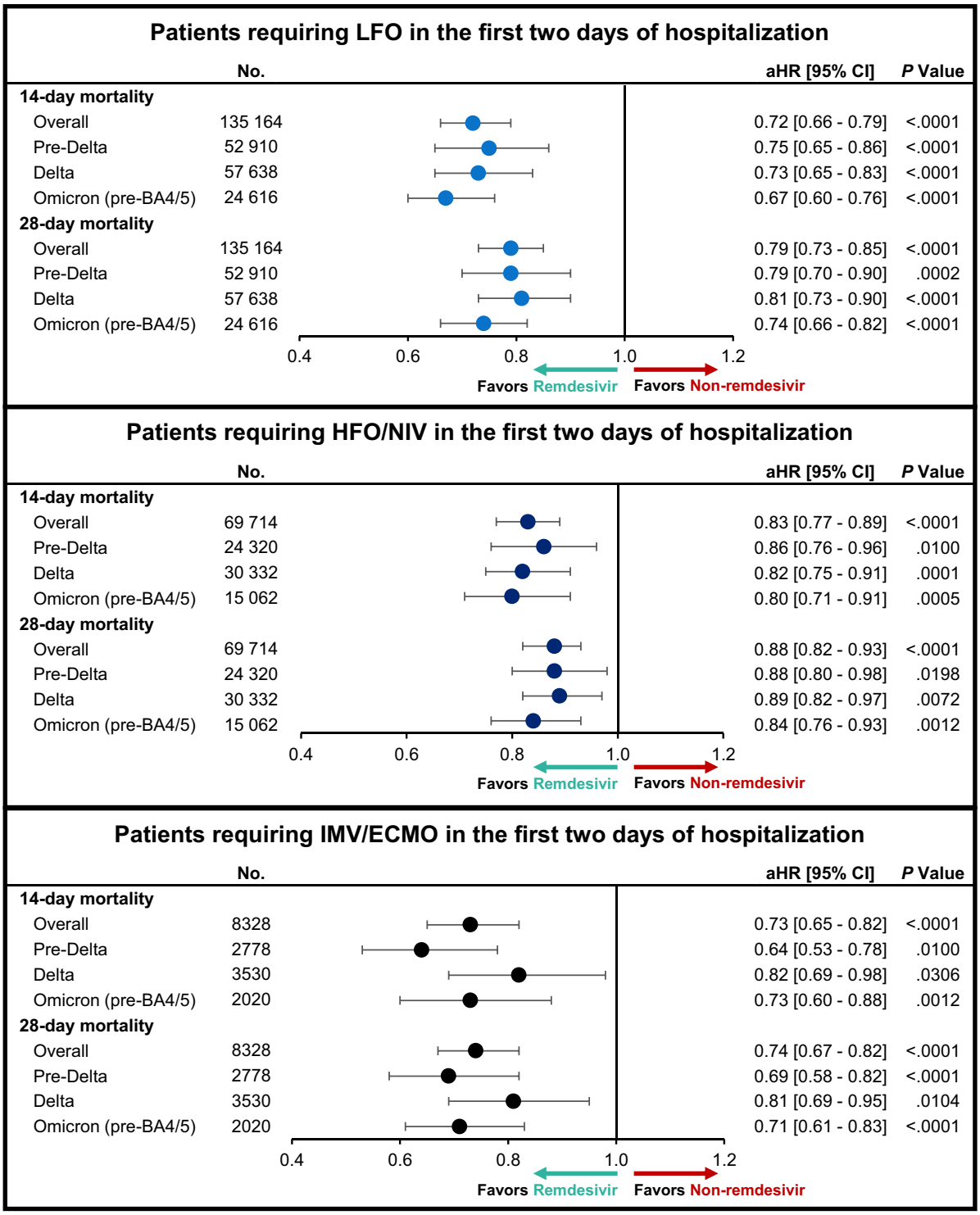

Figure 3. Fourteen- and 28-day in-hospital mortality among patients requiring LFO, HFO/NIV, or IMV/ECMO across the COVID-19 variant periods (adjusted Cox proportional hazards model). Estimates were adjusted for age, admission month, admission venue (ICU vs. general ward), and baseline concomitant COVID-19 treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab). Abbreviations: aHR, adjusted hazard ratio; HFO/NIV, high-flow oxygen/noninvasive ventilation; ICU, intensive care unit; IMV/ECMO, invasive mechanical ventilation/membrane oxygenation; LFO, low-flow oxygen.

Following matching, the HFO/NIV study cohort comprised 34 857 remdesivir-treated patients and 10 189 unique non-remdesivir patients, weighted to 34 857 non-remdesivir patients following 1:1 matching with replacement. There were no covariates with an absolute standardized difference value of >0.1 following matching (Table 1).

Across VOC periods, 5853 (16.8%) remdesivir-treated and 6770 (19.4%) non-remdesivir patients died within 14 days. By 28 days, 9009 (25.8%) remdesivir-treated and 9853 (28.3%) matched non-remdesivir patients had died. In the unadjusted analysis, risk of mortality was significantly lower in remdesivir-treated patients compared with non-remdesivir patients (log-rank test: $P < .0001$) (Figure 2). After adjustment for covariates, remdesivir treatment was associated with a significant reduction in mortality compared with non-remdesivir use among patients requiring HFO/NIV at baseline (14-day aHR, 0.83; 95% CI, 0.77–0.89; 28-day aHR, 0.88; 95% CI, 0.82–0.93) (Figure 3). The significant reduction in mortality associated with remdesivir treatment was observed across VOC periods (Figure 3).

IMV/ECMO Patients

After applying the inclusion and exclusion criteria, there were 8723 patients who required IMV/ECMO upon admission, including 4961 (56.9%) patients administered remdesivir within 2 days of hospitalization and 3762 (43.1%) not administered remdesivir during hospitalization for COVID-19 (Figure 1).

Before matching in the IMV/ECMO cohort, remdesivir-treated patients were more likely to be obese (54.0% vs. 45.4%) and were more likely to have been administered corticosteroids (96.1% vs. 87.2%) and/or convalescent plasma (10.1% vs. 3.1%) at baseline compared with non-remdesivir patients (Table 1).

Following matching, the IMV/ECMO cohort comprised 4164 remdesivir-treated patients and 1880 unique non-remdesivir patients, weighted to 4164 non-remdesivir patients following 1:1 matching with replacement. After matching, all covariates were well balanced between remdesivir-treated and non-remdesivir patients with an absolute standardized difference ≤ 0.10 (Table 1).

Across VOC periods, a total of 1157 (27.8%) remdesivir-treated and 1470 (35.3%) non-remdesivir patients died within 14 days. By 28 days, 1724 (41.4%) remdesivir-treated and 2105 (50.6%) non-remdesivir patients had died. In the unadjusted analysis, risk of mortality was significantly lower in remdesivir patients compared with non-remdesivir patients (log-rank test: $P < .0001$) (Figure 2). After adjustment for covariates, remdesivir treatment was associated with a significant reduction in mortality compared with non-remdesivir treatment (14-day aHR, 0.73; 95% CI, 0.65–0.82; 28-day aHR, 0.74; 95% CI, 0.67–0.82) (Figure 3). These findings were consistent across VOC periods (Figure 3).

DISCUSSION

Although over 3 years have passed since the emergence of severe acute respiratory syndrome coronavirus 2, patients critically ill with COVID-19 still face high mortality rates and have limited therapeutic options [1–3]. In this large, multicenter, retrospective cohort study of routine clinical practice, initiation of remdesivir upon hospital admission was associated with significantly reduced mortality in COVID-19 patients requiring supplemental oxygen upon admission, including those requiring IMV/ECMO. The effectiveness of remdesivir was less pronounced among patients requiring HFO/NIV upon admission vs. patients requiring LFO or IMV/ECMO, but overlapping 95% CIs indicate similar significant survival benefits across these baseline supplemental oxygen requirement groups. Remdesivir was associated with reduced mortality across VOC periods but was most pronounced during the Omicron wave. While the early initiation of antivirals is clearly optimal to decrease risk of inflammatory dysregulation in COVID-19 patients, the window of opportunity to reduce mortality with antiviral treatment may not be fully closed even when patients present later in the disease course.

Randomized controlled trial data have confirmed the effectiveness of early remdesivir administration in reducing time to recovery and mortality among COVID-19 patients in outpatient settings, in hospitalized patients not requiring ventilation, and in patients requiring LFO [5, 6, 12, 13]. For example, a 10-day course of remdesivir was superior to placebo in reducing mortality of hospitalized LFO patients in ACTT-1 (HR, 0.30; 95% CI, 0.14–0.64) [6]. The present analyses and earlier studies demonstrate that the effectiveness of guideline-recommended remdesivir treatment among patients requiring LFO has been consistent since the early part of the pandemic, despite advances in the clinical management of COVID-19 and the emergence of new VOC [5, 14]. However, 33.5% of patients requiring LFO at hospital admission did not receive guideline-recommended treatment with remdesivir, suggesting a missed opportunity to administer an efficacious therapy from which patients may have benefitted.

The effectiveness of remdesivir in patients requiring HFO, NIV, IMV, or ECMO has been more uncertain, in part related to the small proportion of critically ill patients enrolled in the trials. For HFO/NIV patients, there is evidence to support clinical benefits associated with remdesivir use. In patients requiring LFO or HFO in the SOLIDARITY trial, risk of mortality was significantly reduced among remdesivir patients compared with the control group (rate ratio, 0.87; 95% CI, 0.76–0.99) [5]. In the previous PINC AI Healthcare Database study, a significant reduction in mortality was observed at 14 days in remdesivir-treated patients compared with non-remdesivir patients on HFO/NIV (14-day aHR, 0.81; 95% CI, 0.70–0.83; 28-day aHR, 0.97; 95% CI, 0.84–1.11) between August and November 2020 [10]. In the present analyses, in which the study sample is likely to have reduced heterogeneity due to the focus on patients hospitalized with a primary diagnosis of COVID-19, the benefits of remdesivir were observed even up to 28 days. Another US-based real-world study found evidence that patients with severe

disease, defined as requiring higher levels of respiratory support, also had reduced time to clinical improvement with remdesivir treatment (median [IQR], 8.0 [6.0–13.0] days; vs. median [IQR], 9.0 [5.5–16.0] days; aHR, 1.59, 95% CI, 1.02–2.49) [9].

For patients requiring IMV/ECMO, the ACTT-1 and SOLIDARITY trials did not detect a significant effect of remdesivir on patients with COVID-19 who required ventilation at baseline; however, neither trial was designed or powered for subgroup analysis to evaluate the effectiveness of remdesivir among patients requiring ventilation (invasive or noninvasive) [6, 15]. However, the absence of an interaction between remdesivir treatment and baseline oxygenation in ACTT-1 indicates similar effectiveness of remdesivir regardless of baseline supplemental oxygenation requirement [6]. Furthermore, four large, real-world studies found evidence of benefits from remdesivir in critically ill as well as immunocompromised patients [9–11, 16]. In the previous PINC AI Healthcare Database study, a significant reduction in mortality was observed in remdesivir-treated patients compared with non-remdesivir patients (14-day aHR, 0.70; 95% CI, 0.58–0.84; 28-day aHR, 0.81; 95% CI, 0.69–0.94) among a subgroup of 2592 patients requiring IMV/ECMO between August and November 2020 [10]. Taken together, these findings add to the growing body of evidence to indicate that remdesivir improves survival outcomes in patients with severe or critical COVID-19 disease.

The strengths of the present study include the large population size, which enabled the assessment of the effectiveness of remdesivir across VOC periods. This multicenter database of routine clinical practice included public and private hospitals across 48 states, thereby ensuring that the findings are broadly generalizable to COVID-19 patients hospitalized in the US. These analyses also accounted for a wide range of covariates including baseline COVID-19 medication use, comorbidities, and admission diagnoses. Lastly, initiating follow-up at the same time for both the remdesivir and non-remdesivir groups prevented the occurrence of immortal time bias, following the homogenizing event of admission for a primary diagnosis of COVID-19 flagged as "present on admission."

The primary limitation of this and other comparative effectiveness studies is the potential for residual confounding and subsequent indication bias. Remdesivir patients may have been systematically different than non-remdesivir patients according to unmeasured characteristics. To minimize the risk of confounding by indication, robust propensity score methods and covariate adjustments were employed using an extensive list of clinically relevant covariates. Notably, this data set did not permit determination of prehospital care such as antivirals or other therapeutics administered before hospitalization, which may have led to residual confounding. However, since outpatient remdesivir use was approved by the Food and Drug Administration only in January 2022 and the effect of remdesivir was consistent across VOC time periods before and after this approval, the impact of this limitation on the study's findings is negligible. Furthermore, the database holds information for laboratory values such as estimated glomerular filtration rate only for the subset of patients admitted to hospitals that have opted to share this data. To assess whether renal function was a confounder between the 2 groups, baseline creatinine values, only available for 25% of the patients in the matched cohort, were compared and found to be similar in the 2 matched groups.

Data on vaccinations were not available in this database, in part due to the decentralized nature of the US national vaccination campaign and the nature of this data set. However, the clinical decision to prescribe remdesivir to patients hospitalized for COVID-19 does not typically account for vaccination status given that hospitalization and potential progress of the viral infection have already occurred. As the percentage of vaccinated individuals in the general total US population increased with subsequent VOC periods, the inpatient survival benefit of remdesivir was maintained. This consistency of remdesivir benefits, particularly during the Omicron wave in which a majority of the population was already vaccinated, suggests that this limitation is unlikely to have impacted the study findings meaningfully. Lastly, the study period was until April 2022, so it covered the BA.1 and BA.2 period. The effectiveness of remdesivir against later VOC would warrant future research.

Based on the current evidence, remdesivir should be administered as soon as possible in patients hospitalized for COVID-19 to prevent progression to severe or critical disease. Yet, this study has demonstrated that one-third of LFO patients were not administered remdesivir upon admission, highlighting the considerable room for improvement in the expanded implementation of guideline recommendations to maximize the provision of life-saving therapy to all patients who meet the criteria. Where early remdesivir administration is not possible, robust findings from this study demonstrate that remdesivir administration is associated with a survival benefit even when the hyperinflammatory response has already developed as in patients requiring HFO/NIV or IMV/ECMO. Given the growing evidence supporting the clinical and survival benefits associated with remdesivir use in both severe and critically ill COVID-19 patients, clinical guidelines may merit further revisions.

Supplementary Data

Supplementary materials are available at *Open Forum 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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Author contributions. All listed authors have contributed to the manuscript substantially and have agreed to the final submitted version.

Data availability. The data that support the findings of this study are available from PINC AI™ (https://www.pinc-ai.com). Restrictions apply to the availability of these data, which were used under license for this study.

Ethics approval and consent to participate. An ethics approval and informed consent were not required for this study. This analysis of data from the PINC AI Healthcare Database (formerly Premier Healthcare Database) was conducted under an exemption from Institutional Review Board oversight for US-based studies using de-identified health care records, as dictated by Title 45 Code of Federal Regulations (45 CFR 46.101(b)(4)).

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Potential conflicts of interest. E.M., E.L., C.D.T., R.G., M.B., and S.H. report employment at and being stockholders of Gilead Sciences during the conduct of the study. A.C. and S.H.R. report funding for study/medical writing provided to their institution (Certara) by Gilead Sciences during the conduct of the study. R.L.G. reports grants or contracts to his institution from Eli Lilly, Gilead, Johnson and Johnson, Pfizer, Regeneron, and Roivant Sciences (Kinevant Sciences), participation on advisory boards and consulting fees from AbbVie, Eli Lilly, Gilead Sciences, GSK Pharmaceuticals, and Roche, participation on an advisory board for AstraZeneca, payment or honoraria for lectures/speaking from Gilead Sciences and Pfizer (the latter unrelated to infectious diseases), travel support from Gilead Sciences, de minimis investment in AbCellera, and a gift-in-kind to his institution from Gilead Sciences to facilitate an unrelated academic-sponsored clinical trial (NCT03383419). A.K. reports grants from the National Institutes of Health Adaptive COVID-19 Treatment Trial. C.C.M. reports payment or honoraria for lectures/speaking from AstraZeneca and participation on an advisory board for Gilead Sciences.

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