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Real-World Safety and Effectiveness of Remdesivir and Corticosteroids in Hospitalized Patients with COVID-19

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Abstract: Real-world effectiveness studies of remdesivir in hospitalized patients with COVID-19 conducted to date have produced conflicting findings which may be due, in part, to treatment heterogeneity within standard of care comparison groups. Our objective was to evaluate the comparative effectiveness and safety of remdesivir in a cohort of patients all treated with corticosteroids. We conducted a retrospective cohort study in the National Veterans Affairs Healthcare System. We included hospitalized patients (>18 years old) with positive COVID-19 PCR tests and COVID-19 diagnosis codes, and corticosteroid treatment within 2 days of admission, from 1 May 2020 to 30 November 2021. Time-to-event outcomes included time to inpatient mortality (primary), discharge, mortality after discharge, readmission, and acute kidney injury and bacterial infection after treatment initiation. Propensity score (PS)-adjusted, PS-matched, and inverse probability of treatment weighted (IPTW) Cox proportional hazards regression models controlled for study timeframe, supplemental oxygen, vaccination status, and other important confounders. We observed significantly lower inpatient mortality, 90-day post-discharge mortality, 30-day post-discharge readmission, and significantly longer hospital stays in the remdesivir group (n = 14,509) compared with the non-remdesivir group (n = 4365). Higher rates of bacterial infections were observed in the remdesivir group. Acute kidney injury was lower in subgroup analyses restricting the study population to index dates in 2021, on supplemental oxygen, and fully vaccinated, and higher in those without baseline supplemental oxygen. When comparing the effectiveness and safety of remdesivir plus corticosteroids to a homogenous comparison group, all also treated with corticosteroids, mortality and readmission were significantly lower in the remdesivir group. Longer length of stay corresponds with duration of remdesivir treatment and may impact the risk of developing infections during the hospitalization, which requires further study.

Keywords: COVID-19 treatment; remdesivir; comparative effectiveness; safety; corticosteroids

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1. Introduction

The novel coronavirus SARS-CoV-2, the virus responsible for the coronavirus-19 (COVID-19) pandemic, continues to have a significant burden, causing severe infection, hospitalization, and death worldwide. There is an ongoing need for treatment options to improve clinical outcomes in patients with COVID-19. Remdesivir, a novel nucleotide analog that inhibits SARS-CoV-2 viral replication, is fully approved by the United States (U.S.) Food and Drug Administration (FDA) for adults and pediatric patients with COVID-19 regardless of severity [1]. The World Health Organization has a conditional recommendation for the use of remdesivir in patients with severe COVID-19 but not in patients with critical COVID-19, such as those on mechanical ventilation (invasive or non-invasive) or vasopressor therapy [2]. The Infectious Diseases Society of America (IDSA) and National

Institutes of Health (NIH) similarly recommend remdesivir in hospitalized patients with severe COVID-19 but not in those who require mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [3,4]. Data from clinical trials have not consistently demonstrated a major clinical benefit for all hospitalized patients treated with remdesivir [5–8].

Real-world effectiveness studies have also generated conflicting results regarding the benefits of remdesivir in patients hospitalized with COVID-19, with and without supplemental oxygen, with several studies showing reduced time to clinical improvement [9–12] and another showing shorter duration of mechanical ventilation and shorter length of stay among critically ill patients requiring mechanical ventilation [13]. Other studies show no association or longer duration of hospitalization [14,15] and no impact on mortality with remdesivir [10,14–16]. There are several limitations to previous studies, including completion early in the pandemic (i.e., ended March 2020) [17] and before widespread vaccination in the U.S. (i.e., ended December 2020–March 2021) [10,14,16,18], smaller study populations (53–1200 patients) [14–17,19], short duration of follow-up (up to 28–30 days or discharge) [10,14,16–18], missing data before and after hospitalization [10,14,16–18], and single hospital analyses [14,16].

Another major limitation of previous studies is that the standard of care for COVID-19 continues to evolve [20], and most studies to date have not required standard of care with corticosteroids, monoclonal antibodies, immunomodulating agents, antivirals, and/or any other therapies found to be effective against COVID-19 [10,14–17]. The comparison groups for these studies have been simply those "not receiving remdesivir", with no minimal requirement for any other COVID-19 treatments [10,14–17]. These studies have therefore assumed that patients not receiving remdesivir are receiving a shared standard of care. However, shared standard of care was not verified, resulting in treatment heterogeneity within the comparison groups utilized in each of these studies, as well as the inclusion of patients not receiving appropriate treatment [10,14–17].

International recommendations for corticosteroids in patients with COVID-19 and progressive deterioration of oxygenation were set in March 2020, and in the U.S. by August (NIH) and September 2020 (IDSA) for critically ill patients who require mechanical ventilation or supplemental oxygenation [3,4,21,22]. Regardless of changing recommendations, corticosteroids have remained a mainstay in hospitalized patients with COVID-19, with or without oxygenation. A literature review and meta-analysis of 52 clinical trials found that 27.9% of patients with severe COVID-19 were treated with corticosteroids, and another study of hospitalized patients with COVID-19 revealed that 42.1% received corticosteroids [23,24]. Only one sensitivity analysis compared patients who received both remdesivir and dexamethasone to matched patients who received dexamethasone alone, which showed a statistically significant benefit in clinical improvement associated with remdesivir, particularly for those on room air and low-flow oxygen [10]. Additionally, few studies have assessed safety outcomes [5] and secondary outcomes associated with remdesivir, such as secondary bacterial infections. One retrospective cohort study among patients with COVID-19 from a single hospital revealed that patients treated with remdesivir had a lower likelihood of acute kidney injury but not acute liver injury [16].

As such, real-world evidence is still urgently needed for hospitalized patients with COVID-19, with varied oxygen requirements, particularly comparisons of remdesivir and verified minimal standard of care treatments. In light of the limited existing literature, our study sought to assess the impact of remdesivir on inpatient mortality and secondary effectiveness and safety outcomes in the national Veterans Affairs (VA) Healthcare System among a cohort of patients hospitalized with COVID-19 and all treated with corticosteroids.

2. Materials and Methods

2.1. Data Sources

We conducted a retrospective cohort study in the national VA Healthcare System. We utilized the Veterans Health Administration (VHA) Corporate Data Warehouse and VHA COVID-19 Shared Data Resource, which contain health information from electronic health

records and other administrative systems, including data on hospitalizations and outpatient visits, inpatient and outpatient pharmacy data (including barcode administration data, pharmacy dispensing data, and non-VA medications), inpatient and outpatient diagnoses (International Statistical Classification of Diseases, Tenth Revision, Clinical Modification codes), laboratory and microbiology results, vital signs and vital status, and other health factors, such as COVID-19 symptoms and smoking status. This study was approved by the Institutional Review Board and Research and Development Committee of the VA Providence Healthcare System.

2.2. Study Population

We included hospitalized patients >18 years old with positive COVID-19 PCR tests between 1 May 2020 and 30 November 2021 in the national VA Healthcare System. We excluded non-veterans and patients testing positive more than 2 days after admission or admitted more than 10 days after a positive PCR test. The index date was defined as the date of the first positive PCR test or inpatient admission date, whichever occurred first. Patients with index dates which did not correspond with the test or admission date were excluded. Further exclusions included transfer from another hospital, death or discharge in the first 2 days of admission, pregnancy, length of stay >100 days, no primary or secondary diagnosis of COVID-19, no baseline supplemental oxygen information, no record of any medications dispensed/administered during the hospitalization, and clinical trial patients. Only patients receiving corticosteroids in the first 2 days of admission were included in our study. For those with more than one admission meeting these inclusion and exclusion criteria during the study period, only the first admission was selected for inclusion. Those initiating treatment with remdesivir in the first 2 days of admission were selected for the remdesivir treatment group and those not receiving remdesivir treatment during the admission made up the comparison group (Figure 1).

2.3. Outcomes

The primary outcome was time to inpatient mortality. The secondary time-to-event effectiveness and safety outcomes assessed included time to intensive care unit (ICU) discharge, acute kidney injury (AKI), bacterial infection, fungal infection, hospital discharge, 30-day, 60-day, and 90-day mortality from discharge, and readmission. For AKI, baseline serum creatinine was assessed in the seven days prior to admission until remdesivir initiation for the remdesivir group or corticosteroid initiation for the corticosteroid group. The highest value during that time period was selected as the baseline. If baseline serum creatinine was missing or >1.3 mg/dL, then patients were excluded from the assessment of this outcome. Follow-up serum creatinine was assessed from one day after remdesivir initiation for the remdesivir group or corticosteroid initiation for the corticosteroid group until discharge. AKI was defined as a serum creatinine increase of 1.5 times the baseline serum creatinine or an absolute value >1.5 mg/dL. Bacterial infection and fungal infections were defined as positive clinical cultures collected from one day after remdesivir initiation for the remdesivir group or corticosteroid initiation for the corticosteroid group until discharge. Patients were followed until 31 December 2021 (allowing for at least 30 days of follow-up from inclusion end date of 30 November 2021) or their date of death, whichever occurred sooner.

2.4. Variables

We assessed patient demographics including age, sex, race, body mass index, and treating facility. Symptoms in the 30 days prior to initial clinical presentation included abdominal pain, chills, cold, cough, diarrhea, dyspnea, fatigue, fever, headache, loss of smell, loss of taste, myalgia, rhinorrhea, and sore throat. Medical history over the previous two years included conditions of the Elixhauser and Charlson comorbidity score, and other important medical history, including smoking and alcohol/drug dependence and previous infections, such as pneumonia and influenza. Exposure mapping methods were utilized

to identify other medications received by the patient prior to the index date and during the admission.

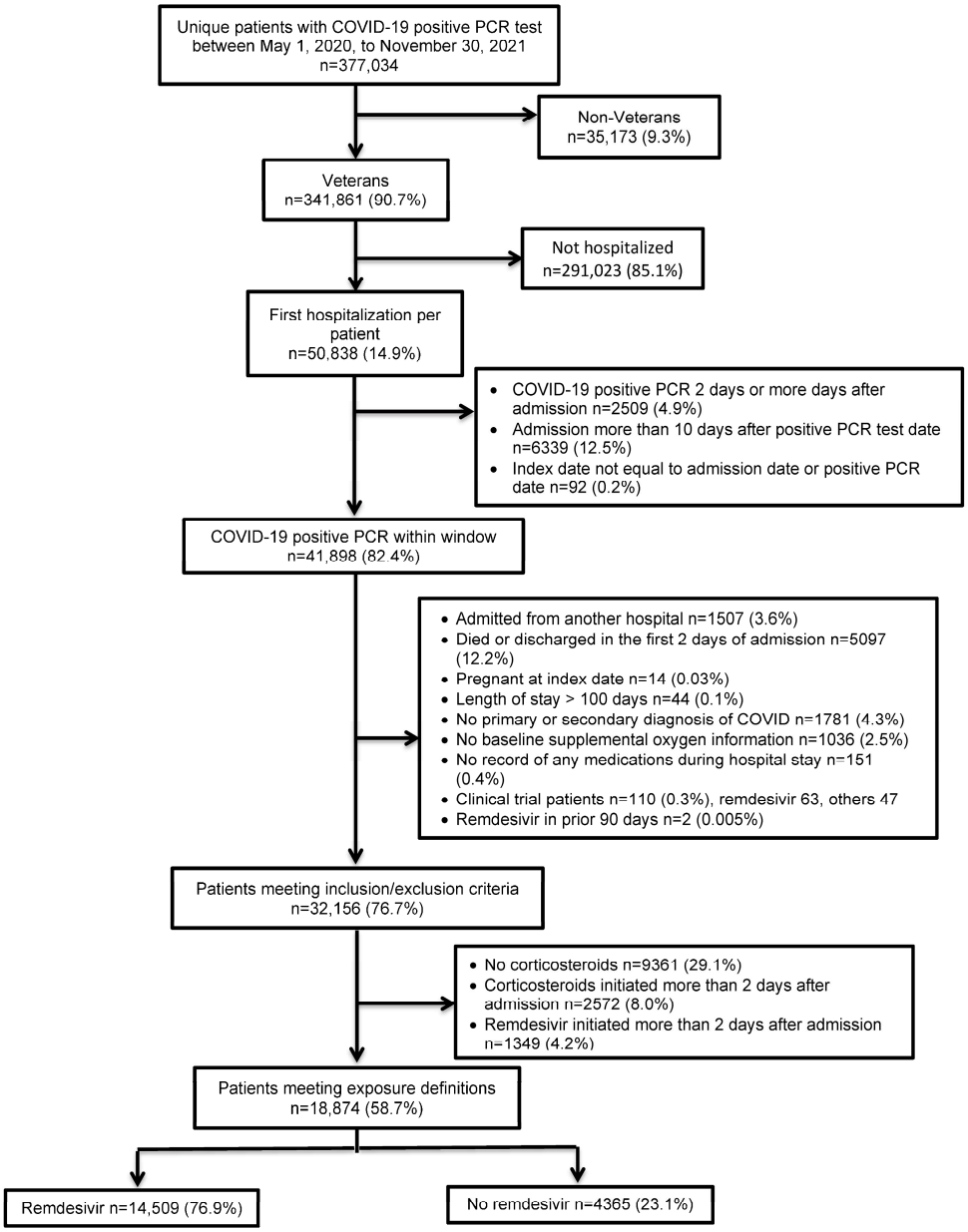

Figure 1. Study population.

2.5. Statistical Analyses

Patient characteristics and comorbidities were assessed to identify potentially confounding baseline characteristics that may differ between the treatment groups. Categorical data were analyzed using X2 or Fisher's exact test. Student's *t*-test or Mann–Whitney U test was used for continuous variables of interest.

We utilized propensity score methods to balance baseline covariates predictive of treatment with corticosteroids and remdesivir vs. corticosteroids without remdesivir. We built an unconditional logistic regression model to derive propensity scores using manual backward elimination modeling [25,26]. Variables which differed significantly between the treatment groups or between those with or without the study outcomes were considered as potential confounders and assessed for inclusion in the propensity score model, including demographics and clinical characteristics, medical history, symptoms, as well as previous medications in the 90 days prior to the index date, baseline medications administered on

the day of admission or day after admission, and concomitant medications administered during remdesivir treatment for the remdesivir group or during corticosteroids treatment for the corticosteroid group. Clinically important variables were forced into the model and included age, facility, obesity/severe obesity, month and year of index date, race, ethnicity, sex, admission source, treating specialty, vaccination status, smoking status/history, rural residence, baseline oxygen status, and Charlson and Elixhauser comorbidity indices in the 2 years prior to the index date [25]. Propensity score assumptions were assessed along with model fit, model discrimination, and multicollinearity [25,27–29]. Covariate balance was assessed with standardized differences [30,31].

Separate Cox proportional hazards regression models were developed to quantify differences in time-to-event effectiveness and safety outcomes of the treatment approaches for each of the aforementioned outcomes. Cox proportional hazards model assumptions, including that of proportionality, were evaluated with formal tests and graphical displays [32]. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated using propensity score adjustment (quintiles), propensity score matching (nearest neighbor matching within a caliper of 0.0001), and inverse probability of treatment weighting [26,27,33–35].

Sensitivity analyses included assessment of time-to-event outcomes additionally controlling for specific concomitant corticosteroids, anticoagulants, and antibiotics, and corticosteroid duration in Cox proportional hazard models. Subgroup analyses included assessment of effectiveness and safety outcomes by timeframe of the index date (1 May 2020–31 December 2020 and 1 January 2021–30 November 2021), by baseline oxygenation status (no supplemental oxygen, supplemental oxygen, non-invasive ventilation, mechanical ventilator or extracorporeal membrane oxygenation (ECMO)), and by vaccination status (fully vaccinated, partially vaccinated, boostered, unvaccinated). All analyses were conducted using SAS (Version 9.2, SAS Institute Inc., Cary, NC, USA).

3. Results

We included 18,874 patients from 120 hospitals (Figure 1).

Demographics and clinical characteristic differences between groups are shown in Table 1. Patients in the remdesivir group were younger (mean age 66.7 years, standard deviation (SD) 13.8 vs. mean 68.9 years, SD 13.5) than those in the non-remdesivir group. Patients receiving remdesivir were more likely to be obese (42.4% vs. 36.3%) and severely obese (10.7% vs. 8.2%), with a higher mean body mass index (BMI) in the remdesivir group (31.3, SD 7.2 vs. 29.7, SD 7.2). Those in the remdesivir group were more likely to be treated in the ICU during admission (4.4% vs. 5.7%) and to receive supplemental oxygen at baseline (76.0% vs. 66.3%). Patients in the remdesivir group were less likely to be fully vaccinated for COVID-19 (11.7% vs. 15.2%) and more likely to have had no prior COVID-19 vaccination (85.5% vs. 82.2%) than those in the non-remdesivir group. Mean duration of corticosteroids differed by only a day between the remdesivir and non-remdesivir groups (mean 7.5 days, SD 5.5 vs. 6.2 days, SD 5.5) in matched analyses.

Medical history differences between groups are shown in Table 2. Patients in the remdesivir group had a lower Charlson comorbidity index (median 2, interquartile range (IQR) 0–4 vs. 3, IQR 1–5) but higher Elixhauser score (median 4, IQR 0–14 vs. 9, IQR 0–21) than those in the in the non-remdesivir group. Those in the remdesivir group were less likely to have a history of diabetes (45.7% vs. 48.5%), hypertension (72.6% vs. 78.1%), cardiovascular disease (44.0% vs. 53.7%), chronic liver disease (8.2% vs. 9.2%), chronic lung disease (39.4% vs. 43.5%), chronic kidney disease (30.2% vs. 45.8%), dementia (6.1% vs. 9.4%), and cancer (23.9% vs. 26.5%) than those in the non-remdesivir group.

Table 1. Baseline demographics and clinical characteristics among patients treated with remdesivir-based regimens vs. non-remdesivir based regimens, overall and propensity score-matched groups.

	Overall			**Matched**		
Demographics	**Remdesivir N = 14,509**	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Age (years), mean (SD)	**66.7 (13.8)**	**68.9 (13.5)**	−0.16	68.2 (13.5)	68.4 (13.6)	−0.02
BMI, mean (SD)	**31.3 (7.2)**	**29.7 (7.2)**	0.22	**30.6 (7.1)**	**30.1 (7.3)**	0.06
Severe obesity (BMI ≥40)	**1540 (10.7%)**	**357 (8.2%)**	0.08	307 (9.3%)	304 (9.2%)	0
Obesity (BMI ≥30)	**6136 (42.4%)**	**1579 (36.3%)**	0.13	1253 (37.9%)	1256 (37.9%)	0
Male	13,705 (94.5%)	4144 (94.9%)	−0.02	3168 (95.3%)	3150 (94.7%)	0.02
Race						
White	**9960 (68.6%)**	**2802 (64.2%)**	0.09	2208 (66.4%)	2247 (67.6%)	−0.02
Black/African American	**3053 (21.0%)**	**1172 (26.9%)**	−0.14	799 (24.0%)	773 (23.3%)	0.02
Asian	**155 (1.1%)**	**30 (0.7%)**	0.04	26 (0.8%)	25 (0.8%)	0
All other	1341 (9.2%)	361 (8.3%)	0.03	292 (8.8%)	280 (8.4%)	0.01
Hispanic or Latino	**1442 (9.9%)**	**389 (8.9%)**	0.04	293 (8.8%)	279 (8.4%)	0.02
Married	**7664 (52.8%)**	**2168 (49.7%)**	0.06	1704 (51.3%)	1673 (50.3%)	0.02
Admit source						
Direct/outpatient	**14,296 (98.5%)**	**4258 (97.5%)**	0.07	3255 (97.9%)	3262 (98.1%)	−0.02
Nursing home	**213 (1.5%)**	**107 (2.4%)**	−0.07	70 (2.1%)	63 (1.9%)	0.02
Admit specialty						
ICU	2914 (20.1%)	851 (19.5%)	0.01	644 (19.4%)	654 (19.7%)	−0.01
Medicine	10,953 (75.5%)	3263 (74.5%)	0.02	2527 (76.0%)	2506 (75.4%)	0.01
Surgery	**642 (4.4%)**	**251 (5.7%)**	−0.06	154 (4.6%)	165 (5.0%)	−0.02
Rurality						
Urban	10,919 (75.3%)	3279 (75.1%)	0	2480 (74.6%)	2496 (75.1%)	−0.01
Rural	951 (6.6%)	272 (6.2%)	0.01	206 (6.2%)	220 (6.6%)	−0.02
Other/missing	2639 (18.2%)	814 (18.7%)	−0.01	639 (19.2%)	609 (18.3%)	0.02
Patient active in past 24 months	14,164 (97.6%)	4261 (97.6%)	0	3243 (97.5%)	3240 (97.4%)	0.01
Primary care visit in past 18 months	13,584 (93.6%)	4088 (93.7%)	0	3100 (93.2%)	3105 (93.4%)	−0.01
ICU during current admission	**5699 (39.3%)**	**1567 (35.9%)**	0.07	1195 (35.9%)	1231 (37.0%)	−0.02
Healthcare exposures, 30 days prior to admission						
Hospitalization	**187 (1.3%)**	**95 (2.2%)**	−0.07	46 (1.4%)	55 (1.6%)	−0.02
Nursing home	7 (0.05%)	6 (0.1%)	−0.03	<5 (<0.1%)	<5 (<0.1%)	0
Intensive care	**29 (0.2%)**	**18 (0.4%)**	−0.04	6 (0.2%)	10 (0.3%)	−0.02
Infection, 90 days prior to index date [a]						
Bacterial infection	**471 (3.3%)**	**214 (4.9%)**	−0.08	132 (4.0%)	124 (3.7%)	0.01
Fungal infection	**19 (0.1%)**	**13 (0.3%)**	−0.04	<5 (<0.1%)	6 (0.2%)	−0.02
Baseline supplemental oxygen						
Mechanical ventilator/ECMO	586 (4.0%)	188 (4.3%)	−0.01	153 (4.6%)	148 (4.4%)	0.01
Non-invasive ventilator	**1363 (9.4%)**	**315 (7.2%)**	0.08	233 (7.0%)	268 (8.1%)	−0.04
Supplemental oxygen	**11,029 (76.0%)**	**2893 (66.3%)**	0.22	2357 (70.9%)	2381 (71.6%)	−0.02
No supplemental oxygen	**1531 (10.6%)**	**969 (22.2%)**	−0.32	582 (17.5%)	528 (15.9%)	0.04
Vaccine status prior to index date						
Fully vaccinated	**1690 (11.7%)**	**665 (15.2%)**	−0.11	411 (12.4%)	441 (13.3%)	−0.03
Booster	78 (4.6%)	37 (5.6%)	−0.04	19 (4.6%)	23 (5.2%)	−0.02
Partially vaccinated	417 (2.9%)	113 (2.6%)	0.02	90 (2.7%)	86 (2.6%)	0.01
No vaccination	**12,402 (85.5%)**	**3587 (82.2%)**	0.09	2824 (84.9%)	2798 (84.2%)	0.02
Duration of remdesivir mean (SD)	4.9 (1.9)	–		4.8 (1.9)	–	

SD = standard deviation; Std diff = standardized difference, – = none. Data are *n* (%), unless otherwise indicated. Bold indicates statistically significant difference ($p < 0.05$). [a] Bacterial and fungal infections assessed from positive cultures 90 days prior to index date.

Table 2. Medical history among patients treated with remdesivir-based regimens vs. non-remdesivir based regimens, overall and propensity score-matched groups.

	Overall			**Matched**		
Medical History in the 2 Years Prior to Index Date	**Remdesivir N = 14,509**	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Charlson comorbidity index, median (IQR)	**2 (0–4)**	**3 (1–5)**	−0.33	2 (1–4)	2 (1–4)	0.02
Elixhauser score, median (IQR)	**4 (0–14)**	**9 (0–21)**	−0.35	6 (0–17)	6 (0–17)	−0.02
Acute cardiac injury	**521 (3.6%)**	**263 (6.0%)**	−0.11	164 (4.9%)	153 (4.6%)	0.02
Acute liver injury	35 (0.2%)	11 (0.3%)	0	13 (0.4%)	8 (0.2%)	0.03
Acute myocardial infarction	**521 (3.6%)**	**262 (6.0%)**	−0.11	164 (4.9%)	152 (4.6%)	0.02
Acute respiratory failure	**1552 (10.7%)**	**659 (15.1%)**	−0.13	440 (13.2%)	415 (12.5%)	0.02
Acute kidney failure	**1675 (11.5%)**	**908 (20.8%)**	−0.25	484 (14.6%)	540 (16.2%)	−0.05
Acute kidney injury	**3238 (22.3%)**	**1663 (38.1%)**	−0.35	955 (28.7%)	989 (29.7%)	−0.02
Alcohol dependence	2180 (15.0%)	695 (15.9%)	−0.02	534 (16.1%)	540 (16.2%)	0
Anxiety	2452 (16.9%)	758 (17.4%)	−0.01	539 (16.2%)	566 (17.0%)	−0.02
Acute respiratory distress syndrome	17 (0.1%)	9 (0.2%)	−0.02	<5 (<0.1%)	5 (0.1%)	−0.01
Arrhythmia	743 (5.1%)	235 (5.4%)	−0.01	161 (4.8%)	163 (4.9%)	0
Asthma	1144 (7.9%)	338 (7.7%)	0.01	253 (7.6%)	267 (8.0%)	−0.02
Bronchitis	**1338 (9.2%)**	**486 (11.1%)**	−0.06	328 (9.9%)	336 (10.1%)	−0.01
Coronary atherosclerosis and other heart disease	**3905 (26.9%)**	**1481 (33.9%)**	−0.15	986 (29.7%)	1032 (31.0%)	−0.03
Cancer	**3466 (23.9%)**	**1155 (26.5%)**	−0.06	855 (25.7%)	825 (24.8%)	0.02
Cardiomyopathy	**722 (5.0%)**	**313 (7.2%)**	−0.09	209 (6.3%)	194 (5.8%)	0.02
Cerebrovascular disease	**411 (2.8%)**	**175 (4.0%)**	−0.06	129 (3.9%)	115 (3.5%)	0.02
Congestive heart failure	**1945 (13.4%)**	**942 (21.6%)**	−0.22	546 (16.4%)	578 (17.4%)	−0.03
Chronic lung disease	**5715 (39.4%)**	**1897 (43.5%)**	−0.08	1369 (41.2%)	1385 (41.7%)	−0.01
Cirrhosis	**398 (2.7%)**	**203 (4.7%)**	−0.10	124 (3.7%)	118 (3.6%)	0.01
Chronic obstructive pulmonary disease	**3714 (25.6%)**	**1283 (29.4%)**	−0.09	953 (28.7%)	936 (28.2%)	0.01
Cardiovascular disease including hypertension	**6385 (44.0%)**	**2342 (53.7%)**	−0.19	1581 (47.5%)	1632 (48.1%)	−0.03
Dementia	**882 (6.1%)**	**412 (9.4%)**	−0.13	264 (7.9%)	263 (7.9%)	0
Diabetes	**6630 (45.7%)**	**2118 (48.5%)**	−0.06	1518 (45.7%)	1517 (45.6%)	0
Diabetes type I	**271 (4.1%)**	**138 (6.5%)**	−0.08	76 (5.0%)	75 (4.9%)	0
Diabetes type II	6597 (99.5%)	2107 (99.5%)	−0.06	1513 (99.7%)	1509 (99.5%)	0
Non-alcohol drug dependency	**504 (3.5%)**	**230 (5.3%)**	−0.09	152 (4.6%)	143 (4.3%)	0.01
Emphysema	477 (3.3%)	129 (3.0%)	0.02	116 (3.5%)	107 (3.2%)	0.02
Epilepsy	212 (1.5%)	82 (1.9%)	−0.03	56 (1.7%)	53 (1.6%)	0.01
Heart disease	**4933 (34.0%)**	**1909 (43.7%)**	−0.20	1254 (37.7%)	1306 (39.3%)	−0.03
Heart failure	**2329 (16.1%)**	**1101 (25.2%)**	−0.23	651 (19.6%)	677 (20.4%)	−0.02
Human immunodeficiency virus	123 (0.9%)	44 (1.0%)	−0.02	35 (1.1%)	29 (0.9%)	0.02
Hypertension	**10,533 (72.6%)**	**3407 (78.1%)**	−0.13	2469 (74.3%)	2501 (75.2%)	−0.02
Hyperlipidemia	9662 (66.6%)	2891 (66.2%)	0.01	2168 (65.2%)	2185 (65.7%)	−0.01
Inflammatory bowel disease	**510 (3.5%)**	**198 (4.5%)**	−0.05	131 (3.9%)	124 (3.7%)	0.01
Influenza	342 (2.4%)	117 (2.7%)	−0.02	83 (2.5%)	82 (2.5%)	0
Ischemic stroke	**908 (6.3%)**	**381 (8.7%)**	−0.09	248 (7.5%)	240 (7.2%)	0.01
Chronic kidney disease	**4381 (30.2%)**	**1999 (45.8%)**	−0.33	1247 (37.5%)	1249 (37.6%)	0
Liver disease	**1194 (8.2%)**	**402 (9.2%)**	−0.03	295 (8.9%)	267 (8.0%)	0.03
Lower respiratory infection	1340 (9.2%)	446 (10.2%)	−0.03	308 (9.3%)	320 (9.6%)	−0.01
Major depressive disorder	4396 (30.3%)	1310 (30.0%)	0.01	1018 (30.6%)	971 (29.2%)	0.03
Metastatic tumor	**297 (2.1%)**	**149 (3.4%)**	−0.08	93 (2.8%)	85 (2.6%)	0.01
Obesity hypoventilation	160 (1.1%)	42 (1.0%)	0.01	37 (1.1%)	32 (1.0%)	0.01
Obstructive sleep apnea	**5229 (36.0%)**	**1455 (33.3%)**	0.06	1137 (34.2%)	1116 (33.6%)	0.01
Peripheral artery disease	**2234 (15.4%)**	**945 (21.7%)**	−0.16	582 (17.5%)	604 (18.2%)	−0.02
Parkinson's disease	247 (1.7%)	90 (2.1%)	−0.03	53 (1.6%)	65 (2.0%)	−0.03
Pneumonia	**1546 (10.7%)**	**675 (15.5%)**	−0.14	434 (13.1%)	425 (12.8%)	0.01
Post-traumatic stress disorder	2909 (20.1%)	838 (19.2%)	0.02	649 (19.5%)	636 (19.1%)	0.01
Pulmonary heart disease	**595 (4.1%)**	**280 (6.4%)**	−0.10	150 (4.5%)	174 (5.2%)	−0.03
Pulmonary fibrosis	257 (1.8%)	59 (1.4%)	0.03	49 (1.5%)	44 (1.3%)	0.01
Septic shock	**641 (4.4%)**	**308 (7.1%)**	−0.11	182 (5.5%)	194 (5.8%)	−0.02
Smoking status						
Current	**1408 (9.7%)**	**491 (11.3%)**	−0.05	362 (10.9%)	347 (10.4%)	0.01
Former	6801 (46.9%)	1982 (45.4%)	0.03	1555 (46.8%)	1544 (46.4%)	0.01
Venous thromboembolism	**545 (3.8%)**	**235 (5.4%)**	−0.08	143 (4.3%)	150 (4.5%)	−0.01

IQR = interquartile range; Std diff = standardized difference. Data are *n* (%), unless otherwise indicated. Bold indicates statistically significant difference ($p < 0.05$).

Symptoms differences between groups are shown in Table 3. Patients in the remdesivir group were more likely to have new onset cough (61.4% vs. 52.9%), dyspnea (64.4% vs. 58.3%), and fever (55.0% vs. 47.8%) than those in the non-remdesivir group. Medications before hospitalization and during hospitalization are shown in Table 4. Patients in the remdesivir group were less likely to have received previous, baseline, and concomitant immunosuppressants and antibiotics than those in the non-remdesivir group. Patients in the remdesivir group were less likely to have received anticoagulant/antiplatelets (19.1% vs. 25.1%), while baseline and concomitant anticoagulant/antiplatelets were more common in the remdesivir vs. non-remdesivir group.

Table 3. COVID-19 symptoms among patients treated with remdesivir-based regimens vs. non-remdesivir based regimens, overall and propensity score-matched groups.

	Overall			**Matched**		
Symptoms 30 Days Prior to Index Date	**Remdesivir N = 14,509**	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Abdominal pain	**684 (4.7%)**	**256 (5.9%)**	−0.05	177 (5.3%)	172 (5.2%)	0.01
Chills	**1874 (12.9%)**	**385 (8.8%)**	0.13	322 (9.7%)	328 (9.9%)	−0.01
Common cold	**4417 (30.4%)**	**1197 (27.4%)**	0.07	961 (28.9%)	952 (28.6%)	0.01
Cough (new onset)	**8902 (61.4%)**	**2308 (52.9%)**	0.17	1858 (55.9%)	1865 (56.1%)	0.00
Diarrhea	3356 (23.1%)	948 (21.7%)	0.03	721 (21.7%)	725 (21.8%)	0.00
Dyspnea (shortness of breath)	**9343 (64.4%)**	**2545 (58.3%)**	0.13	2031 (61.1%)	2040 (61.4%)	−0.01
Malaise (fatigue)	3995 (27.5%)	1204 (27.6%)	0.00	899 (27.0%)	885 (26.6%)	0.01
Fever (>100.4 F)	**7980 (55.0%)**	**2085 (47.8%)**	0.15	1675 (50.4%)	1666 (50.1%)	0.01
Headache	**3125 (21.5%)**	**676 (15.5%)**	0.16	596 (17.9%)	577 (17.4%)	0.02
Loss of smell	**702 (4.8%)**	**158 (3.6%)**	0.06	137 (4.1%)	132 (4.0%)	0.01
Loss of taste	**1700 (11.7%)**	**368 (8.4%)**	0.11	333 (10.0%)	310 (9.3%)	0.02
Muscle aches (myalgia)	**1531 (10.6%)**	**313 (7.2%)**	0.12	268 (8.1%)	255 (7.7%)	0.01
Nausea/vomiting	**2922 (20.1%)**	**806 (18.5%)**	0.04	648 (19.5%)	622 (18.7%)	0.02
Runny nose (rhinorrhea)	**711 (4.9%)**	**159 (3.6%)**	0.06	109 (3.3%)	132 (4.0%)	−0.04
Sore throat	**1097 (7.6%)**	**255 (5.8%)**	0.07	216 (6.5%)	205 (6.2%)	0.01
No record of symptoms	**1528 (10.5%)**	**633 (14.5%)**	−0.12	398 (12.0%)	447 (13.4%)	−0.04

Std diff = standardized difference. Data are *n* (%). Bold indicates statistical significance ($p < 0.05$).

Table 4. Previous, baseline, and concomitant medications among patients treated with remdesivir-based regimens vs. non-remdesivir based regimens, overall and propensity score-matched groups.

	Overall			**Matched**		
Medications	**Remdesivir N = 14,509**	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Anticoagulant/antiplatelets						
Previous	**2773 (19.1%)**	**1094 (25.1%)**	−0.14	682 (20.5%)	743 (22.4%)	−0.04
Baseline	**13,719 (94.6%)**	**3905 (89.5%)**	0.19	3061 (92.1%)	3064 (92.2%)	0
Concomitant	**14,068 (97.0%)**	**3998 (91.6%)**	0.23	3140 (94.4%)	3167 (95.3%)	−0.04
Corticosteroids						
Previous	**1344 (9.3%)**	**645 (14.8%)**	−0.17	393 (11.8%)	384 (11.6%)	0.01
Baseline	14,509 (100%)	4365 (100%)	0	3325 (100%)	3325 (100%)	0
Concomitant	**14,443 (99.6%)**	**4365 (100%)**	−0.10	**3303 (99.3%)**	**3325 (100%)**	−0.12
Statins						
Previous	7324 (50.5%)	2253 (51.6%)	−0.02	1636 (49.2%)	1658 (49.9%)	−0.01
Baseline	7207 (49.7%)	2191 (50.2%)	−0.01	1640 (49.3%)	1630 (49.0%)	0.01
Concomitant	7469 (51.5%)	2241 (51.3%)	0	1688 (50.8%)	1683 (50.6%)	0

Table 4. *Cont.*

	Overall			**Matched**		
Medications	**Remdesivir N = 14,509**	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Antibiotics						
Previous	**1858 (12.8%)**	**694 (15.9%)**	−0.09	480 (14.4%)	459 (13.8%)	0.02
Baseline	**6027 (41.5%)**	**1959 (44.9%)**	−0.07	1468 (44.2%)	1420 (42.7%)	0.03
Concomitant	**6667 (46.0%)**	**2261 (51.8%)**	−0.12	1638 (49.3%)	1637 (49.2%)	0
NSAIDs						
Previous	4449 (30.7%)	1396 (32.0%)	−0.03	1045 (31.4%)	1036 (31.2%)	0.01
Baseline	**4957 (34.2%)**	**1578 (36.2%)**	−0.04	1195 (35.9%)	1186 (35.7%)	0.01
Concomitant	**5344 (36.8%)**	**1704 (39.0%)**	−0.05	1314 (39.5%)	1283 (38.6%)	0.02
Melatonin						
Previous	**1006 (6.9%)**	**371 (8.5%)**	−0.06	247 (7.4%)	233 (7.0%)	0.02
Baseline	3144 (21.7%)	905 (20.7%)	0.02	704 (21.2%)	664 (20.0%)	0.03
Concomitant	4363 (30.1%)	1259 (28.8%)	0.03	972 (29.2%)	933 (28.1%)	0.03
ACE inhibitors						
Previous	**3756 (25.9%)**	**1052 (24.1%)**	0.04	828 (24.9%)	831 (25.0%)	0
Baseline	**2448 (16.9%)**	**577 (13.2%)**	0.1	511 (15.4%)	470 (14.1%)	0.03
Concomitant	**2901 (20.0%)**	**703 (16.1%)**	0.1	607 (18.3%)	586 (17.6%)	0.02
Histamine H2 antagonists						
Previous	**758 (5.2%)**	**265 (6.1%)**	−0.04	200 (6.0%)	184 (5.5%)	0.02
Baseline	1903 (13.1%)	541 (12.4%)	0.02	450 (13.5%)	409 (12.3%)	0.04
Concomitant	2427 (16.7%)	706 (16.2%)	0.01	566 (17.0%)	536 (16.1%)	0.02
ARBs						
Previous	2138 (14.7%)	675 (15.5%)	−0.02	499 (15.0%)	500 (15.0%)	0
Baseline	1497 (10.3%)	424 (9.7%)	0.02	355 (10.7%)	331 (10.0%)	0.02
Concomitant	1760 (12.1%)	489 (11.2%)	0.03	410 (12.3%)	389 (11.7%)	0.02
Metformin						
Previous	**3285 (22.6%)**	**703 (16.1%)**	0.17	668 (20.1%)	604 (18.2%)	0.05
Baseline	**413 (2.9%)**	**84 (1.9%)**	0.06	84 (2.5%)	74 (2.2%)	0.02
Concomitant	**667 (4.6%)**	**155 (3.6%)**	0.05	140 (4.2%)	135 (4.1%)	0.01
Hydroxychloroquine						
Previous	98 (0.7%)	40 (0.9%)	−0.03	20 (0.6%)	26 (0.8%)	−0.02
Baseline	**62 (0.4%)**	**44 (1.0%)**	−0.07	**14 (0.4%)**	**31 (0.9%)**	−0.06
Concomitant	**68 (0.5%)**	**48 (1.1%)**	−0.07	**14 (0.4%)**	**34 (1.0%)**	−0.07
Antivirals						
Previous	449 (3.1%)	148 (3.4%)	−0.02	109 (3.3%)	104 (3.1%)	0.01
Baseline	385 (2.7%)	114 (2.6%)	0	88 (2.7%)	81 (2.4%)	0.01
Concomitant	410 (2.8%)	118 (2.7%)	0.01	90 (2.7%)	83 (2.5%)	0.01
Interleukin-6 inhibitors						
Previous	<5 (<0.03)	<5 (<0.1%)	−0.03	–	–	–
Baseline	**486 (3.4%)**	**87 (2.0%)**	0.08	78 (2.4%)	73 (2.2%)	0.01
Concomitant	**874 (6.0%)**	**163 (3.7%)**	0.11	141 (4.2%)	141 (4.2%)	0
Immunosuppressants						
Previous	**335 (2.3%)**	**180 (4.1%)**	−0.10	76 (2.3%)	93 (2.8%)	−0.03
Baseline	**175 (1.2%)**	**141 (3.2%)**	−0.14	50 (1.5%)	62 (1.9%)	−0.03
Concomitant	**183 (1.3%)**	**145 (3.3%)**	−0.14	52 (1.6%)	65 (1.9%)	−0.03
Antiparasitic						
Previous	<5 (<0.03)	<5 (<0.1%)	0.02	–	–	–
Baseline	**149 (1.0%)**	**20 (0.5%)**	0.07	19 (0.6%)	15 (0.5%)	0.02
Concomitant	**176 (1.2%)**	**22 (0.5%)**	0.08	24 (0.7%)	18 (0.5%)	0.02

Table 4. *Cont.*

Medications	Overall			Matched		
	Remdesivir N = 14,509	**Non-Remdesivir N = 4365**	**Std Diff**	**Remdesivir N = 3325**	**Non-Remdesivir N = 3325**	**Std Diff**
Janus kinase inhibitors						
Previous	29 (0.2%)	10 (0.2%)	−0.01	7 (0.2%)	10 (0.3%)	−0.02
Baseline	**233 (1.6%)**	**29 (0.7%)**	0.09	34 (1.0%)	29 (0.9%)	0.02
Concomitant	**414 (2.9%)**	**59 (1.4%)**	0.1	53 (1.6%)	58 (1.7%)	−0.01
Casirivimab/imdevimab						
Previous	<5 (<0.03)	<5 (<0.1%)	0.01	–	–	–
Baseline	**30 (0.2%)**	**24 (0.6%)**	−0.06	**11 (0.3%)**	**<5 (<0.2%)**	0.05
Concomitant	**11 (0.1%)**	**21 (0.5%)**	−0.08	<5 (<0.2%)	<5 (<0.2%)	0
Bamlanivimab/etesevimab						
Baseline	**7 (0.05%)**	**14 (0.3%)**	−0.06	<5 (<0.2%)	5 (0.2%)	−0.03
Concomitant	**<5 (<0.03)**	**10 (0.2%)**	−0.06	<5 (<0.2%)	<5 (<0.2%)	0

ACE inhibitor = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; Std diff = standardized difference, – = none. Data are *n* (%). Bold indicates statistically significant difference ($p < 0.05$). Previous medications were in the 90 days prior to the index date. Baseline medications were administered in the first two days of admission. Concomitant medications were during remdesivir treatment for the remdesivir group, or during corticosteroid treatment for the non-remdesivir group.

Propensity score matching eliminated significant differences in the remdesivir and non-remdesivir matched groups, as shown in Tables 1–4 (all standardized differences <0.10; PS model C-statistic 0.71, Hosmer–Lemeshow goodness-of-fit test $p = 0.48$). Only five variables differed significantly in chi-square, Fisher's exact, or *t*-tests after PS-matching; however, all of these standardized differences were less than 10%. Utilization rates of other medications that have been used to treat COVID-19, such as monoclonal antibodies, interleukin-6 inhibitors, janus kinase inhibitors, and hydroxychloroquine, were low and well balanced after matching.

3.1. Time-to-Event Outcomes

We observed significantly lower inpatient mortality (PS-quintile adjusted HR 0.79, 95% CI 0.72–0.87; PS-matched HR 0.70, 95% CI 0.55–0.88; IPTW HR 0.79, 95% CI 0.73–0.85), 90-day post-discharge mortality (PS-quintile adjusted HR 0.77, 95% CI 0.67–0.88; PS-matched HR 0.72, 95% CI 0.58–0.89; IPTW HR 0.82, 95% CI 0.73–0.92), and 30-day post-discharge readmission (PS-quintile adjusted HR 0.80, 95% CI 0.72–0.89; PS-matched HR 0.83, 95% CI 0.71–0.97; IPTW HR 0.86, 95% CI 0.78–0.94) in the remdesivir group (Figure 2; PS model variables in Supplementary Table S1). Remdesivir was also associated with significantly longer hospital stays (PS-quintile adjusted HR 0.86, 95% CI 0.83–0.90; PS-matched HR 0.74, 95% CI 0.69–0.79; IPTW HR 0.86, 95% CI 0.83–0.89, i.e., decreased probability of the event occurring sooner in the remdesivir group compared with the non-remdesivir group) and intensive care stays (PS-matched HR 0.77, 95% CI 0.62–0.95; IPTW HR 0.93, 95% CI 0.88–0.98). In the PS-matched analysis, the median length of stay in the remdesivir group was 5 days (IQR 4–10) vs. 4 days (IQR 3–9) in the non-remdesivir group. Among those admitted to the ICU, the median length of ICU stay in the remdesivir group was 7 days (IQR 4–13) vs. 6 days (IQR 3–12) in the non-remdesivir group in the PS-matched analysis. Higher rates of bacterial infections were also observed in the remdesivir group (PS-quintile adjusted HR 1.15, 95% CI 1.02–1.29; PS-matched HR 1.45, 95% CI 1.17–1.80; IPTW HR 1.10, 95% CI 1.01–1.20, i.e., higher probability of positive bacterial culture after treatment initiation occurring sooner in the remdesivir group compared with the non-remdesivir group). No differences were observed in time to fungal infection or acute kidney injury.

Time-to-event outcomes	No. of events/No. of patients (%)		Hazard ratio (95% CI)
	Remdesivir	Non-remdesivir	
Inpatient mortality			
PS quintile adjusted	1838/14,509 (12.7%)	620/4365 (14.2%)	**0.79 (0.72–0.87)**
PS matched	440/3325 (13.2%)	465/3325 (14%)	**0.70 (0.55–0.88)**
IPTW	1838/14,509 (12.7%)	620/4365 (14.2%)	**0.79 (0.73–0.85)**
30-day mortality			
PS quintile adjusted	485/12,671 (3.8%)	240/3745 (6.4%)	**0.76 (0.65–0.90)**
PS matched	125/2885 (4.3%)	166/2860 (5.8%)	**0.70 (0.54–0.90)**
IPTW	485/12,671 (3.8%)	240/3745 (6.4%)	**0.80 (0.69–0.92)**
60-day mortality			
PS quintile adjusted	635/12,671 (5.0%)	316/3745 (8.4%)	**0.76 (0.66–0.88)**
PS matched	161/2885 (5.6%)	217/2860 (7.6%)	**0.69 (0.55–0.86)**
IPTW	635/12,671 (5.0%)	316/3745 (8.4%)	**0.81 (0.71–0.91)**
90-day mortality			
PS quintile adjusted	721/12,671 (5.7%)	358/3745 (9.6%)	**0.77 (0.67–0.88)**
PS matched	189/2885 (6.6%)	242/2860 (8.5%)	**0.72 (0.58–0.89)**
IPTW	721/12,671 (5.7%)	358/3745 (9.6%)	**0.82 (0.73–0.92)**
Hospital discharge			
PS quintile adjusted	12,671/14,509 (87.3%)	3745/4365 (85.8%)	**0.86 (0.83–0.90)**
PS matched	2885/3325 (86.8%)	2860/3325 (86.0%)	**0.74 (0.69–0.79)**
IPTW	12,671/14,509 (87.3%)	3745/4365 (85.8%)	**0.86 (0.83–0.89)**
ICU discharge			
PS quintile adjusted	4187/5699 (73.5%)	1083/1567 (69.1%)	0.94 (0.87-1.00)
PS matched	839/1195 (70.2%)	859/1231 (69.8%)	**0.77 (0.62–0.95)**
IPTW	4187/5699 (73.5%)	1083/1567 (69.1%)	**0.93 (0.88–0.98)**
Bacterial infection			
PS quintile adjusted	1618/14,229 (11.4%)	390/4257 (9.2%)	**1.15 (1.02–1.29)**
PS matched	390/3249 (12.0%)	281/3243 (8.7%)	**1.45 (1.17–1.80)**
IPTW	1618/14,229 (11.4%)	390/4257 (9.2%)	**1.10 (1.01–1.20)**
Fungal infection			
PS quintile adjusted	628/14,497 (4.3%)	170/4359 (3.9%)	0.98 (0.82-1.18)
PS matched	136/3322 (4.1%)	122/3321 (3.7%)	0.81 (0.56-1.19)
IPTW	628/14,497 (4.3%)	170/4359 (3.9%)	0.99 (0.85-1.14)
Acute kidney injury			
PS quintile adjusted	479/7886 (6.1%)	73/1784 (4.1%)	1.04 (0.81-1.34)
PS matched	92/1649 (5.6%)	66/1540 (4.3%)	1.00 (0.38-2.66)
IPTW	479/7886 (6.1%)	73/1784 (4.1%)	0.88 (0.74-1.05)
30-day readmission			
PS quintile adjusted	1363/12,671 (10.8%)	578/3745 (15.4%)	**0.80 (0.72–0.89)**
PS matched	341/2885 (11.8%)	397/2860 (13.9%)	**0.83 (0.71–0.97)**
IPTW	1363/12,671 (10.8%)	578/3745 (15.4%)	**0.86 (0.78–0.94)**

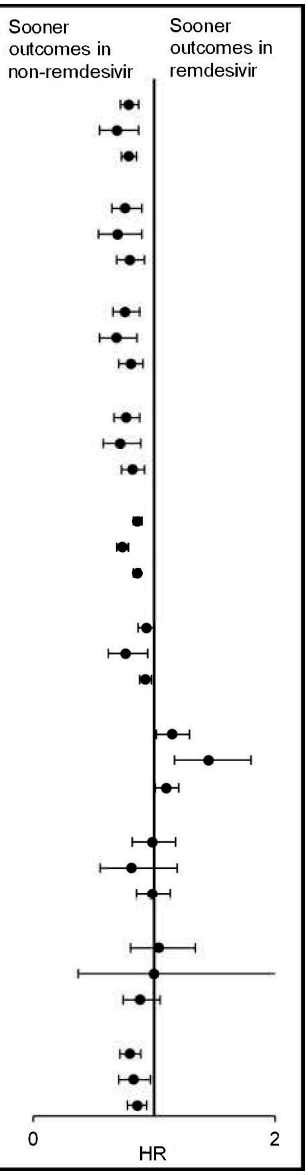

Figure 2. Time-to-event effectiveness and safety outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens vs. non-remdesivir-based regimens. HR = hazard ratio; ICU = intensive care unit; IPTW = inverse probability of treatment weighted; PS = propensity score. Bold indicates statistically significant ($p < 0.05$). The propensity score was derived from an unconditional logistic regression model and controlled for the variables listed below and in Supplementary Table S1. Variables in the propensity score model included age at index date, baseline supplemental oxygen, body mass index, Charlson comorbidity index, current intensive care admission, Elixhauser score, ethnicity, facility indicator, fungal infection 90 days prior to index date, gender, history of acute kidney injury, acute liver injury, alcohol dependence, any diabetes, arrhythmia, Bell's palsy, bipolar disorder, bronchitis, cancer, cardiomyopathy, Cheyne stokes breathing pattern, chronic kidney disease, chronic kidney failure, chronic lung disease, chronic rheumatic heart disease, cirrhosis, congestive heart failure, coronary atherosclerosis and other heart disease, dementia, emphysema, hyperlipidemia, hypertension, major depressive disorder, mild liver disease, nephrosis, non-alcohol drug dependency, obesity hypoventilation, obstructive sleep apnea, other heart disease/ill-defined heart disease, pneumonia, pulmonary fibrosis, schizophrenia, septic shock, sickle cell disease, sleep apnea, sleep related non-obstructive hypoventilation, thalassemia, urinary stones/kidney stones, and

ventilator-associated pneumonia 2 years prior to index date, marital status, medications during admission concomitant with remdesivir in the remdesivir group or concomitant with corticosteroids in the corticosteroid group (angiotensin receptor blockers inhibitors use, angiotensin-converting-enzyme's inhibitors, antibiotics, anticoagulant/antiplatelets, antiparasitic, antivirals, interleukin-6 inhibitors, janus kinase inhibitors, monoclonal antibodies (bamlanivimab/etesevimab, casirivimab/imdevimab), non-steroidal anti-inflammatory drugs and statins), medications during admission prior to remdesivir initiation in the remdesivir group or prior to corticosteroids initiation in the corticosteroid group (angiotensin-converting-enzyme's inhibitors, antibiotics, anticoagulant/antiplatelets, h2 blocker, immunosuppressants, interleukin-6 inhibitors, janus kinase inhibitors, monoclonal antibodies (bamlanivimab/etesevimab, casirivimab/imdevimab), non-steroidal anti-inflammatory drugs and statins), medications used 90 days prior to index date (angiotensin receptor blockers inhibitors, angiotensin-converting-enzyme's inhibitors, antibiotics, corticosteroids, immunosuppressants, interleukin-6 inhibitors, and janus kinase inhibitors), month and year of index date, race, rurality, smoking status, source of admission, symptoms 30 days prior to index date (abdominal pain, chills, cough new onset, diarrhea, fever >100.4 F, headache, loss of smell, malaise/fatigue, and muscle aches/myalgia), treating specialty, and vaccination status.

3.2. Sensitivity and Subgroup Analyses

The results were consistent in sensitivity analyses controlling for concomitant treatment with cefepime, dexamethasone, enoxaparin, heparin, hydrocortisone, meropenem, methylprednisolone, piperacillin-tazobactam, prednisone, and vancomycin (Supplementary Table S2), with two exceptions. Readmission in the 30 days after discharge was only significant in PS-adjusted analyses. Additionally, fungal infection rates were higher in the remdesivir group when controlling for specific antibiotics, anticoagulants, and corticosteroids (PS-adjusted HR 1.42, 95% CI 1.16–1.73; IPTW 1.38, 95% CI 1.18–1.62).

Results in the subgroup analysis by timeframe of the index date, 1 May 2020–31 December 2020 (Supplementary Table S3, n = 7438, 74.4% remdesivir, 25.6% non-remdesivir) and 1 January 2021–30 November 2021 (Supplementary Table S4, n = 11,436, 78.5% remdesivir, 21.5% non-remdesivir), were mostly similar to the main analyses (Figure 2). Exceptions were non-significance of duration of ICU stay and significantly lower AKI (IPTW HR 0.74, 95% CI 0.60–0.92) in the remdesivir group in 2021.

Significantly lower AKI (IPTW HR 0.65, 95% CI 0.52–0.81) in the remdesivir group was also observed among those with baseline supplemental oxygen (Supplementary Table S5, n = 13,922, 79.2% remdesivir, 20.8% non-remdesivir), while higher AKI (IPTW HR 2.20, 95% CI 1.09–4.43) was observed in the remdesivir group among a smaller subgroup of patients with no baseline supplemental oxygen (Supplementary Table S6, n = 2500, 61.2% remdesivir, 38.8% non-remdesivir).

Fewer significant differences were observed in subgroup analyses among those not requiring supplemental oxygen (Supplementary Table S6, n = 2500, 61.2% remdesivir, 38.8% non-remdesivir; significantly lower HR for hospital and ICU discharge and readmission, higher HR for bacterial infection, no differences in mortality), requiring non-invasive mechanical ventilation (Supplementary Table S7, n = 1678, 81.2% remdesivir, 18.8% non-remdesivir; significantly lower HR for hospital discharge, no differences in mortality) or invasive mechanical ventilation/ECMO (Supplementary Table S8, n = 774, 75.7% remdesivir, 24.3% non-remdesivir; significantly lower HR for inpatient mortality and readmission) due to small numbers.

As 84.7% of the study population was unvaccinated, results in the subgroup analysis among the unvaccinated (Supplementary Table S9, n = 15,989, 77.6% remdesivir, 22.4% non-remdesivir) were similar to the main analysis (Figure 2). Among the fully vaccinated (Supplementary Table S10, n = 2355, 71.8% remdesivir, 28.2% non-remdesivir), there were only significant differences in inpatient mortality (IPTW HR 0.62, 95% CI 0.50–0.78), AKI (IPTW HR 0.54, 95% CI 0.31–0.92), length of hospital stay (IPTW HR 0.80, 95% CI 0.73–0.87), and length of ICU stay (IPTW HR 0.82, 95% CI 0.69–0.96).

Results were also similar in sensitivity analyses controlling for corticosteroid duration (Supplementary Table S11), except inpatient mortality, hospital discharge, and ICU discharge results were only significant in the PS-adjusted and IPTW analyses. Bacterial infection results were only significant in the PS-adjusted and matched analyses.

4. Discussion

In our large, national, multicenter, retrospective cohort study among almost 15,000 hospitalized patients with COVID-19, all treated with corticosteroids, mortality and readmission rates were significantly lower among patients treated with remdesivir-based regimens vs. non-remdesivir regimens. Remdesivir inhibits the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication [36]. Remdesivir is a prodrug that is metabolized to the pharmacologically active remdesivir triphosphate [36]. Remdesivir triphosphate is an adenosine triphosphate analogue that competes for incorporation into RNA chains by the SARS-CoV-2 RdRp, resulting in delayed chain termination during viral RNA replication. Remdesivir triphosphate also can inhibit viral RNA synthesis by incorporation into the viral RNA template [36].

In our study, hospital and ICU stays were longer in the remdesivir group, as were rates of bacterial infection compared to those not treated with remdesivir. Importantly, these effects persisted in patients requiring supplemental oxygen and in the unvaccinated, two groups that are especially vulnerable to more serious manifestations of COVID-19. While previous studies have been limited by treatment heterogeneity within the comparison groups and inclusion of patients not receiving appropriate treatment [10,14–17], a major strength of our study is the requirement for a shared standard of care with corticosteroids among patients receiving and not receiving remdesivir. While no differences in AKI rates were observed in the overall population, remdesivir was associated with significantly lower AKI among several subgroups, including those hospitalized in 2021, those fully vaccinated, and those with baseline supplemental oxygen. Alternatively, higher AKI rates were observed among the subgroup of patients without baseline supplemental oxygen, a patient population in which concomitant remdesivir and corticosteroid treatment is not routinely recommended [3,4].

Our findings related to significantly lower inpatient mortality (PS-matched HR 0.70) and lower 30-day mortality (PS-matched HR 0.70) in the remdesivir group are consistent with one previous study, with effect estimates of a similar magnitude. A previous large, multicenter, retrospective cohort study among hospitalized patients diagnosed with COVID-19 between August and November 2020 similarly demonstrated that remdesivir was associated with lower in-hospital mortality at 14 days (PS-matched HR 0.76, 95% CI 0.70–0.83) and 29 days (PS-matched HR 0.89, 95% CI 0.82–0.96) [18]. Though corticosteroid treatment was not an inclusion criterion of this study, after matching, 96.0% of patients in the remdesivir group and 96.8% in the non-remdesivir had received steroids.

Alternatively, another large, multicenter, retrospective cohort study among individuals hospitalized with laboratory-confirmed COVID-19 from February 2020 to February 2021 did not identify a survival benefit with remdesivir in the overall study population [10]. However, in the subgroup of patients on low-flow oxygen, concomitant remdesivir and dexamethasone treatment was associated with significantly lower 28-day mortality rates (PS-matched HR 0.83, 95% CI 0.76–0.91), as compared with dexamethasone alone [10].

In contrast to our findings, another previous multicenter VA study among hospitalized patients with laboratory-confirmed COVID-19 from May to October 2020 found that remdesivir was not associated with lower 30-day mortality (PS-matched HR 1.06, 95% CI 0.83–1.36) [15]. Interestingly, in this study, less than half of the cohort in the matched analysis had received dexamethasone (47.7% in remdesivir recipients and matched controls). In subgroup analyses by dexamethasone treatment, concomitant remdesivir and dexamethasone treatment was not associated with significantly lower 30-day mortality (PS-matched HR 0.93, 95% CI 0.64–1.35; non-dexamethasone PS-matched HR 1.19, 95% CI 0.84–1.69) [15].

A strength of our study is that all patients were treated with standard of care corticosteroids, including dexamethasone and methylprednisolone. Previous studies of remdesivir only assessed dexamethasone use in the remdesivir and comparison groups [10,15]. While dexamethasone is recommended as the agent of choice in COVID-19 patients, methylprednisolone is recommended when dexamethasone is not available [37]. Additionally, current evidence suggests that methylprednisolone has similar beneficial effects as dexamethasone, with some studies demonstrating lower mortality and mechanical ventilation with methylprednisolone compared with dexamethasone [38]. Differential effectiveness and safety with dexamethasone and methylprednisolone is an important area of future study.

Our work also demonstrated improved survival at 90 days post-discharge. As most previous studies have only assessed mortality at 28–30 days, ours is among the first to show an extended survival benefit with remdesivir. Further, remdesivir was associated with a 17% lower readmission rate (PS-matched HR 0.83) in our study. This finding is important, as in the previous national VA cohort of 2179 hospitalizations for COVID-19 early in the pandemic, 27% of survivors were readmitted or died by 60 days after discharge [39]. Our findings are supported by a smaller study among 2062 patients hospitalized with laboratory-confirmed COVID-19 from April to December 2020 in Rhode Island, which found that remdesivir was associated with a 19% decrease in risk of 30-day readmission [40].

Though remdesivir is not currently recommended for patients requiring mechanical ventilation/ECMO, it has been utilized in those patient populations. Our study demonstrated the effectiveness of remdesivir in subgroups of patients with less severe disease; however, we could not assess endpoints in subgroups of patients with more severe disease, such as those on ECMO or invasive mechanical ventilation, due to insufficient sample size. In our study, only 1678 (8.9%) patients had non-invasive mechanical ventilation and 774 (4.1%) had invasive mechanical ventilation or ECMO. As other studies also had few patients with more severe disease and advanced respiratory needs, conflicting findings have been reported in these subgroups of patients. One study suggested that patients with less severe disease (not on oxygen or on low-flow oxygen) may be more likely to benefit from remdesivir than those with more severe disease past the point where anti-viral therapies may be helpful [10]. In the multicenter, retrospective cohort study among individuals hospitalized with laboratory-confirmed COVID-19 from February 2020 to February 2021, higher rates of clinical improvement were observed with remdesivir in the subgroups of patients on room air (PS-matched HR 1.30, 95% CI 1.23–1.41) and low-flow oxygen (PS-matched HR 1.24, 95% CI 1.20–1.28) but not in subgroups with more advanced respiratory support [10]. Importantly, the survival benefit was only observed in those on low-flow oxygen [10]. However, in another study among hospitalized patients diagnosed with COVID-19 (not laboratory-confirmed), remdesivir was associated with improved survival in patients without oxygen (14-day PS-matched HR 0.69, 95% CI 0.57–0.83; 28-day PS-matched HR 0.80, 95% CI 0.68–0.94), on low flow oxygen (14-day PS-matched HR 0.67, 95% CI 0.59–0.77; 28-day PS-matched HR 0.76, 95% CI 0.68–0.86), and in patients with invasive mechanical ventilation/ECMO (14-day PS-matched HR 0.70, 95% CI 0.58–0.84; 28-day PS-matched HR 0.81, 95% CI 0.69–0.94) [18]. In patients on high-flow oxygen or non-invasive ventilation, a lower risk or morality was only found at 14 days (PS-matched HR 0.81, 95% CI 0.70–0.93) and not at 28 days.

We also observed longer hospital stays and ICU stays among patients with remdesivir-based regimens. The median length of stay was 1 day longer in the PS-matched population that received remdesivir as compared with the population that did not. Previous work in the VA has demonstrated significant differences in length of stay, but of a greater magnitude than the difference seen in our study [15]. In the previous VA cohort study from earlier in the pandemic (May to October 2020), remdesivir recipients had a longer median length of hospital stay compared with matched controls (6 days, IQR 4–12 vs. 3 days, IQR 1–7, $p < 0.001$) [15]. This difference in length of stay may be explained by the duration of remdesivir, which is administered intravenously generally for 5 days but may extend up to 10 days based on clinical response and in certain patient populations, particularly among

hospitalized patients with less severe disease not requiring invasive mechanical ventilation or ECMO [1,3,4,15]. We observed significantly longer length of hospital stay in subgroups of patients with and without supplemental oxygen and with non-invasive mechanical ventilation but not in the subgroup with invasive mechanical ventilation/ECMO, which may be due to low numbers. Alternatively, a single-center French study of 325 hospitalized patients with less severe laboratory confirmed COVID-19 pneumonia receiving low-flow oxygen and dexamethasone found no difference in length of stay [18]. The median duration of hospitalization was 9 days in both the remdesivir and non-remdesivir groups ($p = 0.37$). Another small, single-hospital study found no difference in length of stay between the remdesivir and dexamethasone group compared with a historical control group (median 7 vs. 6 days, $p = 0.55$) [14].

In our study, higher rates of culture-confirmed bacterial infections after treatment initiation were observed in the remdesivir group. A previous retrospective cohort study demonstrated a higher frequency of bacteremia in COVID-19 patients treated with remdesivir as compared with matched control patients [41]. Remdesivir is a nucleoside prodrug of an adenosine analog. Adenosine plays a central role in the control of inflammation and might attenuate the host's antimicrobial response, promote bacterial virulence, and consequently facilitate bacterial superinfection [42]. As such, a proposed mechanism for the higher rates of culture-confirmed bacterial infection we observed after remdesivir treatment may be through the alteration of innate and specific immunity by adenosine analogue metabolites of remdesivir, in a similar manner as adenosine [41,43]. However, as infection was a secondary outcome of interest, we did not assess type of organism (e.g., Gram-positive, Gram-negative), type of infection (e.g., bacteremia, pneumonia), type of antibiotic/s (e.g., Gram-negative coverage, Gram-positive coverage), or time to antibiotic initiation in our study. These will be important factors to assess in future research on bacterial infections in patients with COVID-19.

It is also possible that the extended length of hospital and ICU stay observed in the remdesivir group may increase the risk of secondary bacterial infections; however, the difference in median length of stay was only one day in our study. Previous work suggests that secondary bacterial infections in patients with COVID-19 are associated with worse outcomes, including prolonged length of stay [44]. It is also possible that our results are related to the corticosteroid exposure in each group, as mean duration was 1 day longer in the remdesivir group. However, in sensitivity analyses controlling for corticosteroid duration, the results were similar (PS-matched HR 1.37, 95% CI 1.09–1.71). Previous work has shown that the use of corticosteroids is associated with bacterial and fungal infections associated with COVID-19 in ICU patients [45]. Moreover, other work has shown that each day of treatment with steroids increased the odds of BSI by 13% (adjusted odds ratio 1.13, 95% CI 1.04–1.25) in patients with COVID-19 requiring intensive care [46]. Future research will need to further assess this observed association and whether longer length of stay (~1 day) and longer corticosteroid duration (~1 day) affect the risk of secondary bacterial infection in hospitalized patients with COVID-19.

Our study is one of the few real-world comparative effectiveness and safety studies to assess AKI. We found that in the overall population, remdesivir treatment was not associated with AKI. A small, single-center study which included patients hospitalized with COVID-19 in New York City from June 2020 to March 2021 found that patients treated with remdesivir had a significantly lower likelihood of AKI (odds ratio 0.40, 95% CI 0.24–0.67, $p < 0.001$) compared to the non-remdesivir group in the overall cohort [16]. However, this association was not significant in the PS-matched analysis. It appears that corticosteroid use was not controlled for in this study. A multicenter, retrospective chart review assessing remdesivir safety in patients with baseline estimated creatinine clearance (eCrCl) <30 mL/min compared with patients with baseline eCrCl > 30 mL/min found there was no difference in the frequency of AKI (5% vs. 2.5%) [47]. Interestingly, our work suggests that the impact of remdesivir on AKI rates may vary by oxygenation and vaccination status. We are the first to find lower AKI among those with baseline

supplemental oxygen and those fully vaccinated, but higher AKI among those with no baseline oxygen supplementation. Future research is warranted to continue to assess AKI rates in different subgroups of patients with COVID-19.

There are limitations to our observational comparative effectiveness analysis. We used propensity score methods to control for many confounders, but residual confounding may be present due to unmeasured confounders. The utilization of other COVID-19 therapies was low, but well balanced after matching. Next, we only captured medications received outside of the VA system if they were entered into the medication record as non-VA medications. Moreover, we only captured secondary effectiveness and safety outcomes if they occurred in the VA system. We defined bacterial infection and fungal infections as subsequent positive clinical cultures after treatment initiation, but it is possible that positive cultures represent colonization/contamination vs. a true clinical infection. The generalizability of our study may be limited to the VA population, which included mostly older white males. Finally, we implemented three analytic approaches, including PS quintile adjustment, PS matching, and IPTW, with agreement in effect estimates across the three approaches in the overall analysis. However, in several subgroup analyses, the significance of PS-adjusted, PS-matched, and IPTW results may have varied due to small numbers. Our study was conducted prior to authorization of the COVID-19 antivirals, and therefore, they were not assessed in this study.

5. Conclusions

In our large, national, multicenter, retrospective cohort study among almost 15,000 hospitalized patients with COVID-19, laboratory-confirmed with primary/secondary diagnosis, and all treated with corticosteroids, mortality and readmission rates were significantly lower among patients treated with remdesivir-based regimens vs. non-remdesivir regimens, including in high-risk subgroups who were unvaccinated or required baseline supplemental oxygen. Hospital and ICU stays were longer in the remdesivir group, which corresponded with the duration of remdesivir treatment, as were rates of bacterial infection compared to those not treated with remdesivir. While no differences in AKI rates were observed in the overall population, remdesivir was associated with significantly lower AKI among several subgroups, including those hospitalized in 2021, those fully vaccinated, and those with baseline supplemental oxygen. Alternatively, higher AKI rates were observed among the subgroup of patients without baseline supplemental oxygen. Future work in larger cohorts is needed to better understand the impact of remdesivir among those with invasive mechanical ventilation or ECMO. Further research is also needed to determine whether higher rates of culture-confirmed infections after treatment initiation are observed in other patient populations, and whether these differences are related to longer durations of hospital and intensive care stays, longer corticosteroid treatment, and/or other patient and healthcare system factors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid3020015/s1, Tables S1–S11. Table S1: Variables included in the propensity score model, Table S2: Sensitivity analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, Table S3: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, index dates from 1 May 2020 to 31 December 2020 (n = 7438), Table S4: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, index dates from 1 January 2021 to 30 November 2021 (n = 11,436), Table S5: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, supplemental oxygen at baseline (n = 13,922), Table S6: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, no supplemental oxygen at baseline (n = 2500), Table S7: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, non-invasive mechanical ventilation at baseline (n = 1678), Table S8: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, invasive mechanical ventilation/ECMO at baseline (n = 774), Table S9: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, unvaccinated (n = 15,989), Table S10: Subgroup analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, fully vaccinated (n = 2355), Table S11: Sensitivity analyses of time-to-event outcomes among hospitalized patients with COVID-19 and treated with remdesivir-based regimens and non-remdesivir-based regimens, controlling for corticosteroid duration.

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