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Introduction

- Remdesivir (RDV), is a direct-acting nucleotide pro-drug inhibitor of viral RNA-dependent RNA polymerases
 - RDV has been approved by FDA and other regulatory authorities for treatment of hospitalized patients with COVID-19
- Efficacy of RDV was demonstrated in a randomized double-blind, placebo-controlled trial (ACTT-1) which demonstrated improved recovery and other clinical outcomes
- Real world data can complement results from well-controlled trials
 - during a pandemic, where evolution of clinical management can outpace development of new trials
 - when markedly larger sample sizes are needed to assess secondary outcomes or outcomes in important patient subgroups
- This study evaluates the effectiveness of RDV in a large real world dataset of hospitalized COVID-19 patients

Objective

- To evaluate the real-world effectiveness of remdesivir by comparing mortality and hospital discharge in patients exposed to remdesivir versus matched referent patients

Methods

Study design

- We conducted a comparative effectiveness analysis using a matched cohort design in US-based hospital claims data for hospitalized patients with COVID-19 with or without evidence of treatment with remdesivir during their hospital stay according to a pre-specified analytical plan

Data source

- The HealthVerity data ecosystem, which includes de-identified US-based hospital chagemaster, medical and pharmacy claims, laboratory, and EHR data, including Veradigm claims and EHR data, for patients with activity between December 1, 2018 and May 3, 2021

Study population

- The study included patients hospitalized with newly diagnosed COVID-19 between May 1, 2020, the date of RDV emergency use authorization (EUA), and May 3, 2021.

Inclusion criteria

- Any hospitalized patient 18 years of age or older with both of the following:
 - COVID-19 diagnosis on their hospitalization record
 - Minimum of 12 months enrollment or claims prior to index date, with at least 1 medical encounter during this period

Exclusion criteria

- Patients with evidence of being treated in a clinical trial at any time
- Patients with evidence of a prior COVID-19 inpatient hospitalization
- Use of RDV prior to EUA

Matched Comparator

- RDV-exposed patients were matched 1:1 to referent patients using a 2-stage process to ensure covariate balance:
 - Risk-Set Sample (RSS) matching** to ensure exact balance on key covariates, including
 - Calendar time
 - Patient demographics (age, gender)
 - COVID-19 disease severity (baseline oxygen requirement and ICU status)
 - Number of days between admission and RDV exposure
 - Corticosteroid use

- Propensity Score (PS) matching** was then conducted to control for confounding using nearest neighbor matching with a ±1% caliper
 - Patient demographics
 - Clinical characteristics
 - Comorbidities
 - Concomitant medications

- PS matching was repeated for each baseline oxygen support subgroup for estimation of subgroup-specific effects

Index date (follow-up start)

- Exposed cohort: RDV initiation date
- Matched referent cohort: index date of the matched exposed patient

Follow-up end

- The RSS procedure ensures that a patient treated with RDV by a certain point during hospital admission is matched to a similar patient who could have been treated with RDV at the same point during hospital admission but was not. Thus, the matched referent group includes not only patients who

Methods (cont'd)

- were never exposed to RDV, but also patients who were exposed to RDV later in their hospitalization than their matched RDV exposed patient. Taking this into account, end of follow-up was defined in two ways:
 - Primary: As-treated (AT): Patients were censored on earliest of outcome, death, discharge, maximum of 28 days, and RDV crossover date (referent patients only)
 - Sensitivity: Intention to treat (ITT): Patients were censored on earliest of outcome, death, discharge, and maximum of 28 days

Statistical analysis

Outcomes

- Primary outcome:** All-cause mortality
- Secondary outcome:** Hospital discharge

Subgroup analysis

- We evaluated subgroups of patients by baseline oxygen requirement status, which previous research has shown is an indicator of disease severity:
 - room air
 - low-flow oxygen
 - high-flow oxygen or non-invasive ventilation (NIV)
 - invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)

Analysis and software

- Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) for the effectiveness of RDV were reported using the PS-matched exposed cohort compared to the matched referent cohort
- Similar to the approach of Garibaldi et al., a landmark analysis approach was adopted for the secondary outcome (hospital discharge), with follow-up lagged to start at Day 5 to account for patients completing the full 5-day treatment course of RDV
 - As an exploratory analysis, the secondary outcome was also examined without the 5-day landmark
- Results were presented overall and by each baseline oxygen support subgroup
- All analyses were conducted using the Aetion Evidence Platform, which has been previously validated

Key Definitions

COVID-19	Medical Claims or a hospital diagnosis with ICD-10 COVID-19, virus identified
Exposure: Remdesivir*	<ul style="list-style-type: none"> Reported hospital encounter with Charge Code (Vendur/Standard): set string includes remdesivir Procedure Code: C91.0 (V0423), V0424 (V0423), V0425 (V0423)
Primary outcome: Mortality	Reported hospital encounter with Discharge Status: EXPIRES/EXPIRES HOME (HOSPICE), EXPIRES/MEDICAL FACILITY (HOSPICE)
Secondary outcome: Discharge	<ul style="list-style-type: none"> Medical Claims or inpatient hospital encounter with Discharge Status DISCHARGED TO HOME OR SELF CARE (ROUTINE DISCHARGE) Among patients who did not experience the outcome, the discharge (either) or crossover (Days 5-4 from admission - follow up lagged to Day 5)
Baseline Oxygen Requirement Subgroups**	<ul style="list-style-type: none"> Medical Claims or inpatient hospital encounter with Discharge Status DISCHARGED TO HOME OR SELF CARE (ROUTINE DISCHARGE)
Room air	Identifies that the following procedures did not occur: Endotracheal High-flow oxygen, Non-invasive ventilation, Low-flow oxygen
Low-flow or Any Oxygen	<ul style="list-style-type: none"> Low-flow oxygen Any oxygen, including high-flow, low-flow, NIV, IMV or ECMO
High-flow or Non-invasive	<ul style="list-style-type: none"> Non-invasive ventilation High-flow oxygen
Invasive mechanical or ECMO	<ul style="list-style-type: none"> Identifies that the following procedures did occur: ECMO, Invasive mechanical ventilation

* Measured during the inpatient hospitalization
** Measured during and prior to the inpatient hospitalization
*** Measured RDV start/stop date

Covariates Used for RSS- and PS-matching

RSS-matching	<ul style="list-style-type: none"> calendar date (±3 days) of RDV initiation of exposed patient age category of exposed patient sex of exposed patient time (categorized days) since hospital admission of exposed patient ICU status and day prior status of exposed patient Oxygen support level of exposed patient Corticosteroid use on index date and day prior
PS-matching	<ul style="list-style-type: none"> demographic (sex, age, region) obesity oxygen support* ICU status number of days since hospitalizations comorbidities smoking factors affecting health status selected medications

* Oxygen support status was not included in the PS-matching for the oxygen support subgroup analysis.

Results

Patient Characteristics

- Among 60,704 eligible patients in the balanced RSS cohort, 24,856 patients receiving RDV were PS-matched to 24,856 referent patients (Figure 1)
- Demographic and clinical characteristics were well balanced between the exposed and matched referent groups, with absolute standardized differences all <0.10 (Table 1, Table 2, Table 3)

Figure 1. Patient disposition

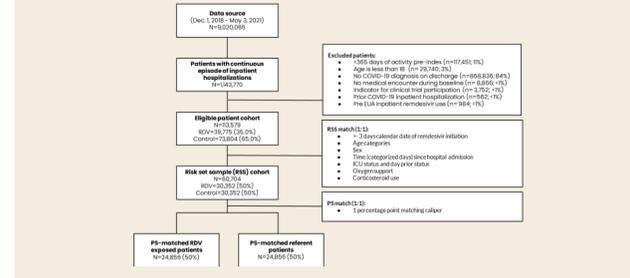


Table 1. Baseline patient characteristics

Demographic Characteristics	RSS Cohort		Propensity score-matched patients		Absolute standardized difference
	RSS-matched RDV (N=24,856)	RSS-matched referent (N=24,856)	PS-matched RDV (N=24,856)	PS-matched referent (N=24,856)	
Age					0.001
Mean (sd)	68.81 (6.32)	68.80 (6.37)	68.84 (6.42)	68.76 (6.37)	
Median [IQR]	67.00 (57.00, 77.00)	67.00 (57.00, 77.00)	68.00 (57.00, 77.00)	67.00 (57.00, 77.00)	
Gender					0.005
Female, n (%)	14,444 (58.1%)	14,444 (58.1%)	14,017 (56.4%)	14,066 (56.6%)	
Male, n (%)	10,412 (41.9%)	10,412 (41.9%)	10,833 (43.6%)	10,790 (43.4%)	
Unknown, n (%)	411 (1.6%)	411 (1.6%)	343 (1.4%)	329 (1.3%)	
Region					0.004
Northwest, n (%)	6,885 (27.7%)	6,885 (27.7%)	6,802 (27.4%)	6,898 (27.8%)	
Midwest, n (%)	2,371 (9.3%)	2,371 (9.3%)	2,322 (9.3%)	2,361 (9.5%)	
South, n (%)	13,782 (53.8%)	13,782 (53.8%)	13,235 (53.3%)	13,889 (56.0%)	
West, n (%)	8,514 (32.1%)	8,514 (32.1%)	8,221 (32.9%)	8,225 (33.0%)	
Other/Missing/Unknown, n (%)	11 (0.0%)	11 (0.0%)	6 (0.0%)	6 (0.0%)	
Oxygen Support Status					0.004
Room air, n (%)	16,446 (66.2%)	16,446 (66.2%)	16,947 (68.2%)	16,947 (68.2%)	
Low-flow, n (%)	6,650 (26.8%)	6,650 (26.8%)	6,434 (25.9%)	6,402 (25.8%)	
High-flow or NIV, n (%)	3,405 (13.6%)	3,405 (13.6%)	2,706 (10.9%)	2,721 (10.9%)	
ECMO/IMV, n (%)	952 (3.8%)	952 (3.8%)	769 (3.1%)	768 (3.1%)	

Table 2. Selected baseline comorbidities

Baseline clinical covariates based on ICD-10	RSS Cohort		Propensity score-matched patients		Absolute standardized difference
	RSS-matched RDV (N=24,856)	RSS-matched referent (N=24,856)	PS-matched RDV (N=24,856)	PS-matched referent (N=24,856)	
Infection, n (%)	15,493 (62.4%)	15,493 (62.4%)	15,493 (62.4%)	15,493 (62.4%)	0.001
Blood (n (%))	11,522 (46.4%)	11,522 (46.4%)	11,522 (46.4%)	11,522 (46.4%)	0.004
Diabetes, n (%)	12,244 (49.2%)	12,244 (49.2%)	12,244 (49.2%)	12,244 (49.2%)	0.002
Metabolic, n (%)	23,249 (93.6%)	23,249 (93.6%)	23,249 (93.6%)	23,249 (93.6%)	0.002
Obesity, n (%)	10,249 (41.2%)	10,249 (41.2%)	10,249 (41.2%)	10,249 (41.2%)	0.001
Endocrine, n (%)	7,884 (31.7%)	7,884 (31.7%)	7,884 (31.7%)	7,884 (31.7%)	0.002
Digestive, n (%)	13,717 (55.2%)	13,717 (55.2%)	13,717 (55.2%)	13,717 (55.2%)	0.001
Neurologic, n (%)	16,302 (65.6%)	16,302 (65.6%)	16,302 (65.6%)	16,302 (65.6%)	0.002
Circulatory, n (%)					
- Ischemic heart disease, n (%)	8,266 (33.3%)	8,266 (33.3%)	8,266 (33.3%)	8,266 (33.3%)	0.003
- Hypertension, n (%)	24,404 (98.1%)	24,404 (98.1%)	24,404 (98.1%)	24,404 (98.1%)	0.002
- Other and unspecified disorders of the circulatory system, n (%)	7,772 (31.3%)	7,772 (31.3%)	7,772 (31.3%)	7,772 (31.3%)	0.003
- Other forms of heart disease, n (%)	10,682 (43.0%)	10,682 (43.0%)	10,682 (43.0%)	10,682 (43.0%)	0.006
- Heart failure, n (%)	5,279 (21.2%)	5,279 (21.2%)	5,279 (21.2%)	5,279 (21.2%)	0.014
- Conductive disorders, dysrhythmias n (%)	7,687 (30.9%)	7,687 (30.9%)	7,687 (30.9%)	7,687 (30.9%)	0.004
Respiratory, n (%)					
- Bronch (Asthma), n (%)	6,824 (27.5%)	6,824 (27.5%)	6,824 (27.5%)	6,824 (27.5%)	0.001
- Bronch (COPD), n (%)	6,814 (27.4%)	6,814 (27.4%)	6,814 (27.4%)	6,814 (27.4%)	0.005
- Obstructive, n (%)	13,638 (54.9%)	13,638 (54.9%)	13,638 (54.9%)	13,638 (54.9%)	0.002
Respiratory, n (%)	23,203 (93.3%)	23,203 (93.3%)	23,203 (93.3%)	23,203 (93.3%)	0.001
Musculoskeletal, n (%)	9,385 (37.8%)	9,385 (37.8%)	9,385 (37.8%)	9,385 (37.8%)	0.004
Smoking, n (%)	8,800 (35.4%)	8,800 (35.4%)	8,800 (35.4%)	8,800 (35.4%)	0.001
Musculoskeletal/Connective Tissue, n (%)	17,890 (71.9%)	17,890 (71.9%)	17,890 (71.9%)	17,890 (71.9%)	0.006
Neoplasms, n (%)	6,402 (25.8%)	6,402 (25.8%)	6,402 (25.8%)	6,402 (25.8%)	0.002
Other signs/symptoms, n (%)	20,468 (82.4%)	20,468 (82.4%)	20,468 (82.4%)	20,468 (82.4%)	0.001

Table 3. Selected baseline concomitant medications

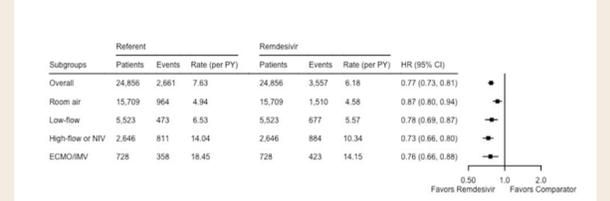
Concomitant medications	RSS Cohort		Propensity score-matched patients		Absolute standardized difference
	RSS-matched RDV (N=24,856)	RSS-matched referent (N=24,856)	PS-matched RDV (N=24,856)	PS-matched referent (N=24,856)	
Corticosteroids, n (%)	21,518 (86.6%)	21,518 (86.6%)	21,518 (86.6%)	21,518 (86.6%)	0.004
HIV protease inhibitors, n (%)	23 (0.1%)	23 (0.1%)	23 (0.1%)	23 (0.1%)	0.003
Hydroxychloroquine/Chloroquine, n (%)	192 (0.8%)	192 (0.8%)	192 (0.8%)	192 (0.8%)	0.004
Immunomodulators, n (%)	728 (2.9%)	728 (2.9%)	728 (2.9%)	728 (2.9%)	0.001
Contraceptive plasma, n (%)	788 (3.2%)	788 (3.2%)	788 (3.2%)	788 (3.2%)	0.002
Interferon, n (%)	23 (0.1%)	23 (0.1%)	23 (0.1%)	23 (0.1%)	0.008
Tocilizumab, n (%)	563 (2.3%)	563 (2.3%)	563 (2.3%)	563 (2.3%)	0.008
Sitagliptin, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Sulfamonomethoxazole, n (%)	4 (0.0%)	4 (0.0%)	4 (0.0%)	4 (0.0%)	0.001
Sulfasalazine, n (%)	146 (0.6%)	146 (0.6%)	146 (0.6%)	146 (0.6%)	0.006
Ribavirin, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.001

Results for Primary Outcome

Mortality

- RDV was associated with a statistically significant reduction in mortality in patients hospitalized with COVID-19 (Figure 2).
- Statistically significant mortality reductions were observed in each subgroup of baseline oxygen requirement

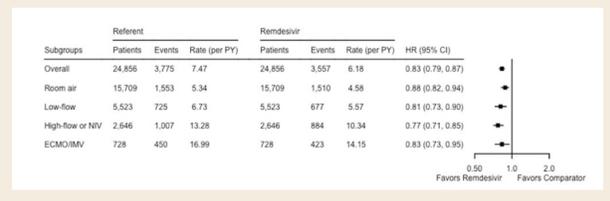
Figure 2. Mortality by baseline oxygen requirement subgroup in the as-treated primary analysis



Mortality

- The statistically significant mortality reduction was also observed in the ITT sensitivity analysis, both overall and by subgroup of baseline oxygen requirement (Figure 3).

Figure 3. Mortality by baseline oxygen requirement subgroup in the intention-to-treat sensitivity analysis



Results for Secondary Outcome

Hospital discharge

- Median (Q1, Q3) observed RDV treatment duration was 5 (4,5) days.
- 5-day landmark analysis showed that treatment with RDV was associated with a statistically significant increased likelihood of hospital discharge, both overall and in patients requiring no oxygen or low-flow oxygen at baseline (Figure 4).
- No discharge benefit was observed in patients on IMV/ECMO at baseline

Figure 4. Hospital discharge with 5-day landmark, by baseline oxygen requirement subgroup in the as-treated primary analysis