Comparative effectiveness of remdesivir and dexamethasone combination therapy vs. dexamethasone monotherapy in patients hospitalised for COVID-19

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Conclusions

- In this study examining patients receiving either RDV+DEX or DEX monotherapy, about half of the patients not requiring supplemental oxygen at baseline, received DEX in the first 2 days of hospitalization despite recommen- dation from guidelines against the use of DEX for these patients[5-7]
- Of the 36,489 patients that received DEX monotherapy at hospital admission:
  - Majority of the patients that did not require any supplemental oxygen at baseline did not require supplemental oxygen therapy throughout the hospitalization but continued receiving DEX after the first two days of hospitalization
  - RDV was not initiated in 37% (n=12,206) of the patients on LFO or 16% (n=5,328) of patients on HFO/NIV during subsequent days in the hospital despite current guideline recommendations to use RDV in these patients
  - Based on the current guidelines from NIH, WHO and IDSA for RDV use in hospitalized patients,[5-7] >50% of the patients that received DEX monotherapy should have also received RDV
- The findings from this study demonstrated that RDV+DEX was associated with a reduction in risk of mortality as compared to DEX monotherapy for the treatment of patients hospitalized for COVID-19 across all levels of baseline supplemental oxygen requirements.
  - The present study provides evidence-based information for following the guidelines recommendations with respect to the use of RDV + DEX in appropriate patient hospitalized for COVID-19

Background

- Despite gradual declines in COVID-19 incidence and mortality, the World Health Organization (WHO) acknowledged that COVID-19 is a continuing threat to lives and health systems in 2024[1]
- The RECOVERY trial conducted in earlier stages of COVID-19 pandemic showed no difference in mortality rates for usual care vs. dexamethasone among patients not requiring supplemental oxygen[2]
- Studies conducted since the RECOVERY study have shown the potential for a detrimental effect of corticosteroid treatment in patients with low-severity COVID-19[3,4]
- National Institutes of Health (NIH), WHO, and Infectious Diseases Society of America (IDSA) treatment guidelines recommend against the use of dexamethasone for COVID-19 patients who do not require supplemental oxygen[5-7]
- Dual therapy with remdesivir (RDV) and dexamethasone (DEX) among patients with COVID-19 demonstrated improved clinical outcomes compared to DEX monotherapy early in the pandemic[8,9]
  - However, there is a lack of real-world evidence on the use of remdesivir + dexamethasone dual therapy versus dexamethasone alone in the more recent COVID-19 era.
- The objective of this study was to examine all-cause mortality in patients hospitalized for COVID-19 initiating RDV+DEX or DEX monotherapy during the Omicron period

Methods

Study Design

- Comparative Effectiveness Retrospective cohort study (**Table 1**)
- Data source: PINC AI Healthcare Database (formerly Premier Healthcare Database)
  - US hospital-based, service-level, all-payer (Commercial, Medicare, Medicaid, others) database
  - Covers ~25% of all US hospitalizations from 48 states
  - Includes patient-level information on billed services for each day of hospitalization
- Baseline is defined as the first two days of hospitalization
- **Primary Endpoints:** 14-day and 28-day all-cause inpatient mortality (defined as a discharge status of "expired" or "hospice")
- Endpoints were examined according to baseline supplemental oxygen requirements: No supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV), and invasive mechanical ventilation (IMV)/ECMO
- Patients were followed from the day after baseline period until day 28 or discharge status of expired or hospice, transfer to another hospital, or addition of RDV after the first 2 days of hospitalization in the DEX monotherapy cohort, whichever was earlier.
  - Following a per-protocol treatment approach, patients were not followed further if RDV was added to the DEX monotherapy group after the first two days of hospitalization.

Statistical Analysis

- All analyses were conducted for the overall study cohort hospitalized during the Omicron time period (December 2021 to April 2023) and stratified by baseline supplemental oxygen requirements (NSOc, LFO, HFO/NIV and IMV/ECMO).
- Propensity scores (PS) were estimated using separate logistic regression models for each baseline supplemental oxygenation requirement group separately
- Covariates used in PS calculation: demographics (age, gender, race, ethnicity), primary payor (commercial, Medicare, Medicaid, other), comorbidities (obesity, diabetes, cancer, chronic obstructive pulmonary disorder cardiovascular [including hypertension], or renal disease), hospital characteristics (bed size, urban or rural, teaching, US region), type of hospital ward on admission (general ward or intensive care unit [ICU]), COVID-19 treatments during baseline (anticoagulants, convalescent plasma, corticosteroids other than dexamethasone), admission month, and admission from a skilled nursing facility.
- Using the derived PS, distribution of underlying confounders in the two treatment groups was balanced using propensity score matching (PSM) as the primary analysis using a 1:1 preferential within-hospital matching approach without replacement with a caliper distance of 0.2 times standard deviation of the logit of the PS was implemented as follows:
  - Patients receiving RDV+DEX were matched to dexamethasone monotherapy patients in the same hospital within the specified caliper distance in the same age group (18-49, 50-64, 65+ years), and admission month groups (two-to-three-month blocks of admission month).
  - The unmatched patients in the RDV+DEX group were then matched to DEX monotherapy patients in another RDV-using hospital of similar bed-size (<200, 200-499, 500+ beds) within the specified caliper distance in same age group (18-49, 50-64, 65+ years), and admission month groups (two-to-three-month blocks of admission month).
- A sensitivity analysis using 1:1 PS matching without replacement was conducted to examine the use of corticosteroids (prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone) instead of only examining dexamethasone
- Cox Proportional Hazards Model was used to assess time to 14- and 28-day mortality adjusting for hospital-level cluster effects, and key covariates: age, admission month, hospital admission ward (documented location for ICU/ Step-down unit vs. general ward), and time-varying covariates for treatment initiated after baseline (baricitinib, tocilizumab, oral antivirals, or corticosteroids other than dexamethasone).

Table 1. Study design

Inclusion criteria	✓ First admission to the hospital Dec 1, 2021-Apr 30, 2023 ✓ Age ≥18 years old ✓ ***Primary* discharge diagnosis of COVID-19** (ICD-10-CM: U07.1) flagged for being "present-on-admission" ✓ **Initiated either RDV+DEX or DEX monotherapy** in the first two days of hospitalization	
Exclusion criteria	✕ Pregnant ✕ Had incomplete/erroneous data fields ✕ Transferred from another hospital or hospice ✕ Admitted for elective procedures ✕ Discharged or died during the baseline period (first two days of hospitalization) ✕ Initiation of other COVID-19 treatments (Baricitinib or Tocilizumab or oral antivirals) at baseline	
	RDV + DEX	**DEX mono**
Treatment	RDV + DEX initiated in first 2 days of admission (baseline)	DEX monotherapy initiated in first 2 days of admission (baseline)

Results

Study Population

- 151,215 patients hospitalized for COVID-19:
  - 61,236 (40%) initiated RDV+DEX in the first 2 days
  - 36,489 (24%) initiated DEX monotherapy in the first 2 days
    - 90% did not receive RDV after the first two days of hospitalization
    - 87% of the patients continued receiving DEX monotherapy after the first two days of hospitalization
    - Of the 15,792 patients that received DEX monotherapy and did not require any supplemental oxygen at baseline, 11,814 (74%) patients did not require supplemental oxygen therapy throughout the hospitalization and 9,641 (61%) continued receiving DEX after the first two days in the hospital
- Before matching:
  - Most patients in the RDV+DEX and DEX monotherapy cohort, respectively, did not receive supplemental oxygen at baseline (43%, 44%), the rest received LFO (37%, 36%), HFO/NIV (18%, 16%), and IMV/ECMO (2%, 4%).
- After 1:1 matching without replacement, 33,037 RDV + DEX patients were matched to 33,037 DEX monotherapy patients (in matching without replacement, matching % is dependent on available patients in the treatment group with smaller sample size)
  - Post-matching balance was achieved across groups of baseline supplemental oxygen with all covariates with a standardized difference absolute value of <0.15
  - Almost half of the patients did not receive supplemental oxygen at baseline (45%), the rest received LFO (37%), HFO/NIV (16%), and IMV/ECMO (2%) (**Table 2**)

Unadjusted Analysis (PS-matched cohort)

- Unadjusted mortality rates at 14- and 28-days were lower for patients receiving RDV+DEX vs. DEX monotherapy across all baseline supplemental oxygen requirements

	PS Matching			
	14-day mortality		28-day mortality	
	Dex Mono	RDV+DEX	Dex Mono	RDV+DEX
NSOc	6.1%	5.6%	7.7%	7.2%
LFO	7.7%	6.1%	9.7%	8.1%
HFO/NIV	15.7%	12.7%	20.7%	17.6%
IMV/ECMO	27.1%	23.5%	35.4%	32.7%

DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc- no supplemental oxygen charges; RDV=remdesivir

Adjusted Analysis (PS-matched cohort)

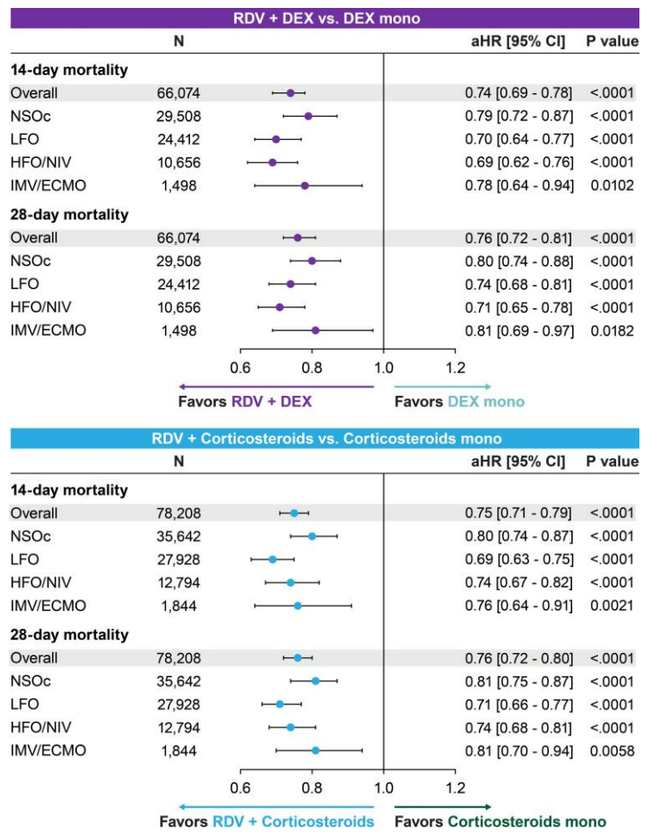
- Using 1:1 propensity score matching without replacement:
  - After adjusting for baseline and clinical covariates, RDV+DEX was associated with a *significantly lower mortality risk* at 14-days and 28-days compared to DEX monotherapy overall and across all supplemental oxygen requirements (**Figure 1**).
- An additional sensitivity analysis conducted to examine the use of corticosteroids (prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone) showed consistent results (**Figure 1**).

Table 2: Baseline characteristics before and after PS matching

		Before matching		After matching	
		DEX mono	RDV + DEX	DEX mono	RDV + DEX
		n=36,489	n=61,236	n=33,037	n=33,037
Age group, years	18-49	8%	10%	8%	8%
	50-64	22%	23%	21%	21%
	65+	70%	67%	72%	72%
Gender	Female	51%	51%	51%	51%
Race	White	77%	78%	78%	78%
	Black	14%	12%	13%	14%
	Asian	2%	2%	2%	2%
	Other	7%	8%	7%	7%
Ethnicity	Hispanic	9%	11%	9%	9%
	Non-Hispanic	84%	82%	84%	84%
	Unknown	7%	6%	7%	7%
Primary Payor	Commercial	14%	17%	14%	14%
	Medicare	72%	69%	73%	72%
	Medicaid	8%	9%	8%	8%
	Other	6%	5%	5%	5%
Hospital size, no. of beds	<100	9%	8%	9%	8%
	100-199	16%	17%	16%	17%
	200-299	21%	20%	21%	21%
	300-399	20%	18%	20%	20%
	400-499	12%	10%	11%	12%
	500+	23%	26%	23%	23%
Comorbidities	Obesity	30%	31%	29%	30%
	Chronic obstructive pulmonary disease	36%	38%	37%	37%
	Cardiovascular disease	88%	85%	88%	88%
	Diabetes	42%	38%	40%	40%
	Renal disease	36%	23%	32%	32%
	Cancer	7%	7%	7%	7%
Immunocompromised condition		16%	17%	16%	16%
Hospital ward on admission	General ward	83%	83%	84%	85%
	ICU/step-down unit	17%	17%	16%	15%
Other treatments at baseline	Anticoagulants	75%	81%	78%	77%
	Convalescent plasma	<1%	<1%	<1%	<1%
	Corticosteroids other than dexamethasone	14%	15%	14%	14%
Baseline supplemental oxygen requirements	NSOc	44%	43%	45%	45%
	LFO	36%	37%	37%	37%
	HFO/NIV	16%	18%	16%	16%
	IMV/ECMO	4%	2%	2%	2%

Note: Baseline was defined as the first two days of the hospitalization
DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; ICU: Intensive Care Unit; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc- no supplemental oxygen charges; RDV=remdesivir

Figure 1: 14- and 28- day mortality in patients hospitalized for COVID-19 by supplemental oxygen requirements: 1:1 propensity score matching without replacement



Note: Estimates adjusted for age, admission month, hospital ward on admission (ICU vs general ward, and time-varying treatment with other COVID-19 medications (baricitinib, tocilizumab, oral antivirals). Adjusted Cox Proportional Hazards model was used to assess 14- and 28-day in-hospital all-cause mortality.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DEX, dexamethasone; HFO/NIV, high flow oxygen/non-invasive ventilation; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation; LFO, low flow oxygen; mono, monotherapy; NSOc, no supplemental oxygen charges; RDV, remdesivir.

References: **1.** WHO. 2024. Available at: https://www.who.int/publications/m/item/covid-19-who-health- emergency-appeal-2024. Accessed 16 January 2024. **2.** Benfield T et al. *Clin Infect Dis* **2021**; 73(11):2031-6. **3.** Marrone A et al. *Clin Infect Dis* **2022**; 75(1): e403-e9. **4.** RECOVERY Collaborative Group, Horby P, et al. *N Engl J Med*. 2021;384(8):693-704. **5.** Crothers K et al. *Eur Respir J* 2022; 60(1). **6.** Pasin L et al. *J Cardiothorac Vasc Anesth* 2021; 35(2): 578-84. **7.** WHO. Therapeutics and COVID-19: living guideline. Available at: https://app.magicapp.org/#/guideline/nBkO1E. Accessed 21 December 2023. **8.** IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ Accessed 21 December 2023. **9.** NIH. COVID-19 Treatment Guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/table-of-contents/ Accessed 21 December 2023.

Disclosures: **EM, MB, TO, JFO**: employee and shareholder (Gilead Sciences, Inc.); **AC**: employee of Certara (contracted by Gilead Sciences, Inc. to conduct the study); **RLG**: advisor (AbbVie, Gilead Sciences, Inc., Eli Lilly, Roche, Johnson & Johnson), consultant (Eli Lilly, Gilead Sciences, Inc., Johnson & Johnson, Kinevant Sciences, Roche), de minimis investment (AbCellera), research contracts (Eli Lilly, Gilead Sciences, Inc., Johnson & Johnson, Pfizer), speaker's bureau (Pfizer); **CCM**: advisor (AstraZeneca, Gilead Sciences, Inc.), speaker's bureau (AstraZeneca, Boehringer Ingelheim), consultant (Gilead Sciences, Inc.); **ANA**: principal investigator or co-investigator (clinical trials sponsored by NIH/NIAID, NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, Alexion), speaker and/or consultant (Pfizer, Salix, Alexion, AstraZeneca, Bayer, Ferring, Seres, Spero, Eli Lilly, Nova Nordisk, Gilead, Renibus, GSK, Dexcom, Reprieve, HeartRite, Aseptiscope)- these relationships are unrelated to the current work; **ACK**: investigator (National Institutes of Health Adaptive COVID-19 Treatment Trial); **PES**: study investigator (Gilead Sciences, ViiV), advisor or review panel member (Gilead Sciences, ViiV, Janssen, Merck)- all of these relationships are unrelated to COVID-19