Remdesivir treatment in patients hospitalized with COVID-19: a comparative analysis of in-hospital all-cause mortality

Essy Mozaffari, Gilead Sciences, Foster City, CA, USA

Authors:
Essy Mozaffari[1], Aastha Chandak[2], Zhiji Zhang[2] ,Shuting Liang[1], Mark Thrun[1], Robert L Gottlieb[5], Daniel R. Kuritzkes[4], Paul E. Sax[4], David Wohl[3], Roman Casciano[2], Paul Hodgkins[1], Richard Haubrich[1]

[1] Gilead Sciences, Foster City, CA; [2] Certara, New York, NY; [3]University of North Carolina, Chapel Hill, NC
[4]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;
[5]Baylor University Medical Center Dallas; Baylor Scott and White Heart and Vascular Hospital; Baylor Scott and White The Heart Hospital Plano, and Baylor Scott and White Research Institute, Dallas, TX

Objective

- Compare survival outcomes for hospitalized COVID-19 patients treated with remdesivir (RDV) vs. those not treated with RDV, adjusting for admission month, hospital factors and patient clinical and demographic characteristics

  - Primary endpoints:
    - 14-day in-hospital mortality
    - 28-day in-hospital mortality

Methods

Study Design
Statistical Analysis
- PS calculation
- Matching
- Baseline checks/diagnostics
- Outcome assessment

Study Design

- Retrospective cohort study used Premier Healthcare Database (US inpatient chargemaster data)
- All baseline variables are examined within the first two days of hospitalization

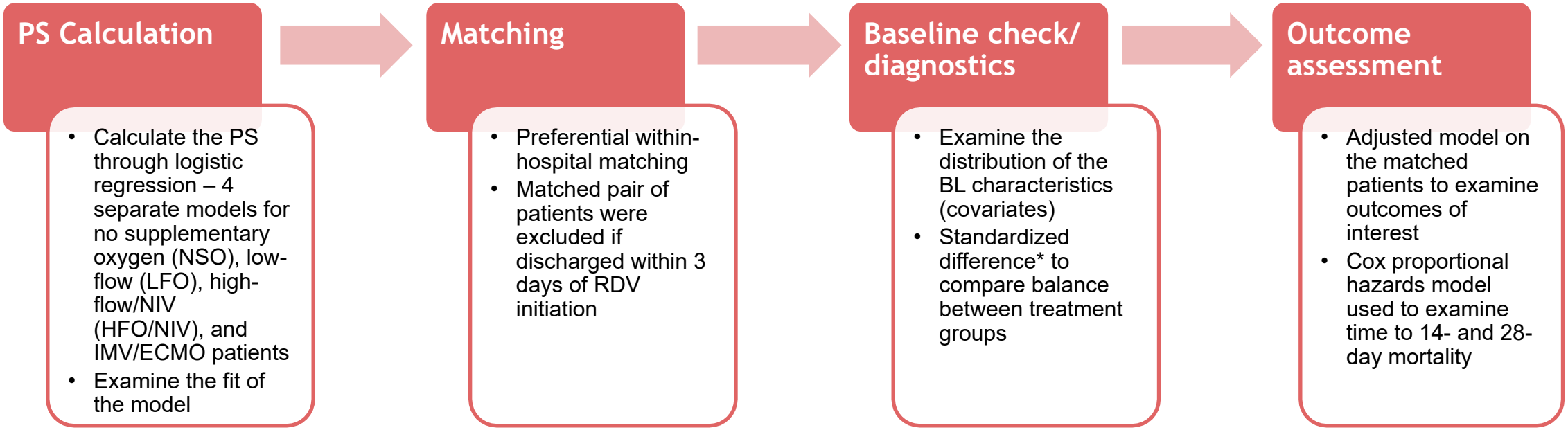
Inclusion criteria	✓ First admission to the hospital **Aug 1-Nov 30**, 2020 ✓ Age ≥18 years old ✓ Primary or secondary discharge diagnosis of COVID-19 (ICD-10-CM: U07.1)
Exclusion criteria	Pregnant Length of stay longer than 100 days Had incomplete data Transferred to or from another hospital Transferred from hospice Admitted for elective procedures Discharged or died during the baseline period (first 2 days of hospitalization) Received RDV as part of a clinical trial or who were first administered RDV after the first two days in the hospital

	RDV cohort	Non-RDV cohort
Treatment	RDV treatment within 2 days of admission	Patients not receiving RDV during the hospitalization

- **Focus on Aug-Nov patients:** based on propensity score distributions of the patients by month; May-Jul patients were distinctly different from the Aug-Nov patients
- **In-hospital mortality:** defined as a discharge status of “expired” or “hospice”

Statistical analysis

- Propensity score (PS) matching approach was used to balance the two groups



BL, baseline; PS, propensity score; RDV, remdesivir; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; NIV, non-invasive ventilation
*Standardized difference is the difference in mean (mean RDV – mean control) divided by the standard deviation of the groups.

Statistical Analysis: PS calculation

Key covariates used in PS calculation

- **Baseline demographics:** age, gender, race, ethnicity, primary payor
- **Key comorbidities:** obesity, COPD, diabetes, renal disease, cardiovascular disease, cancer, immunocompromised condition
- **Hospital characteristics:** bed size, urban/rural, teaching, geographic region
- **Admission month**
- **Admission from SNF**
- **ICU/Step-down/General ward** at baseline
- **Baseline severity** identified through level of oxygenation used at baseline
- **Other indicators of severity** based on admit diagnoses (respiratory failure, hypoxemia, sepsis, pneumonia)
- **Concomitant medications** at baseline: steroids, convalescent plasma, anticoagulants

Baseline=Day 1 or 2 of hospitalization
Patients that died/discharged during the baseline period are excluded

Statistical Analysis: Matching

Preferential Within-Hospital PS Matching

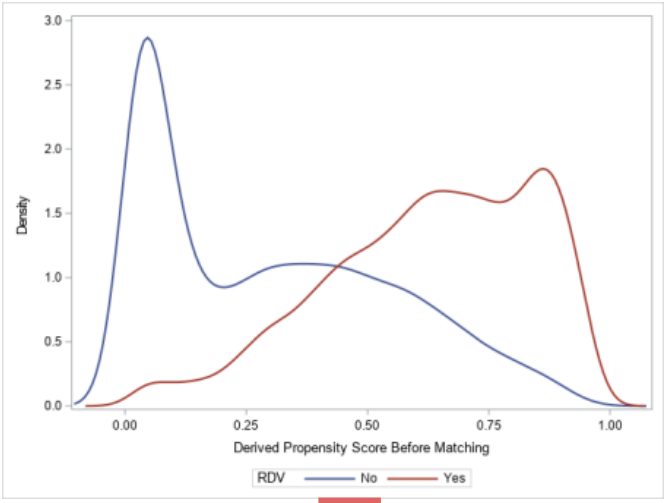
1. PS-matching (caliper=0.2 times standard deviations of the logit of the PS) for patients with same baseline oxygen, within 2-month admission period, within the same hospital

↓ *If unmatched in step 1*

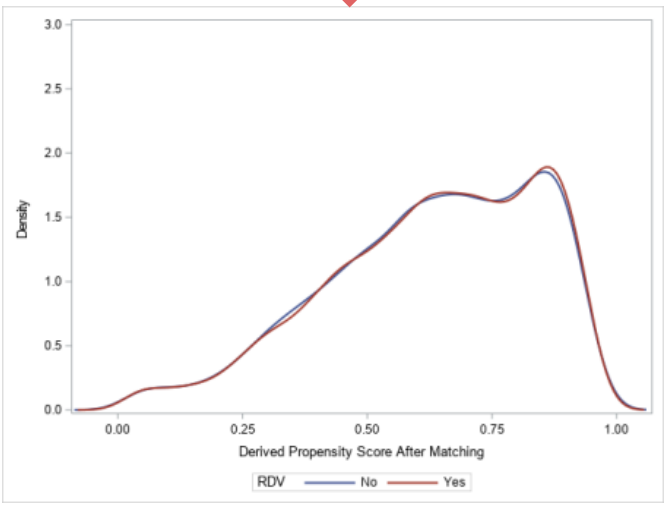
2. PS-matching for patients with same baseline oxygen, within 2-month admission period within another RDV-using hospital of same bed size category

Matched patients were **not discharged within 3 days of index** to emulate ACTT-1 clinical trial exclusion (which excludes anticipated discharges/transfers within 72 hrs)

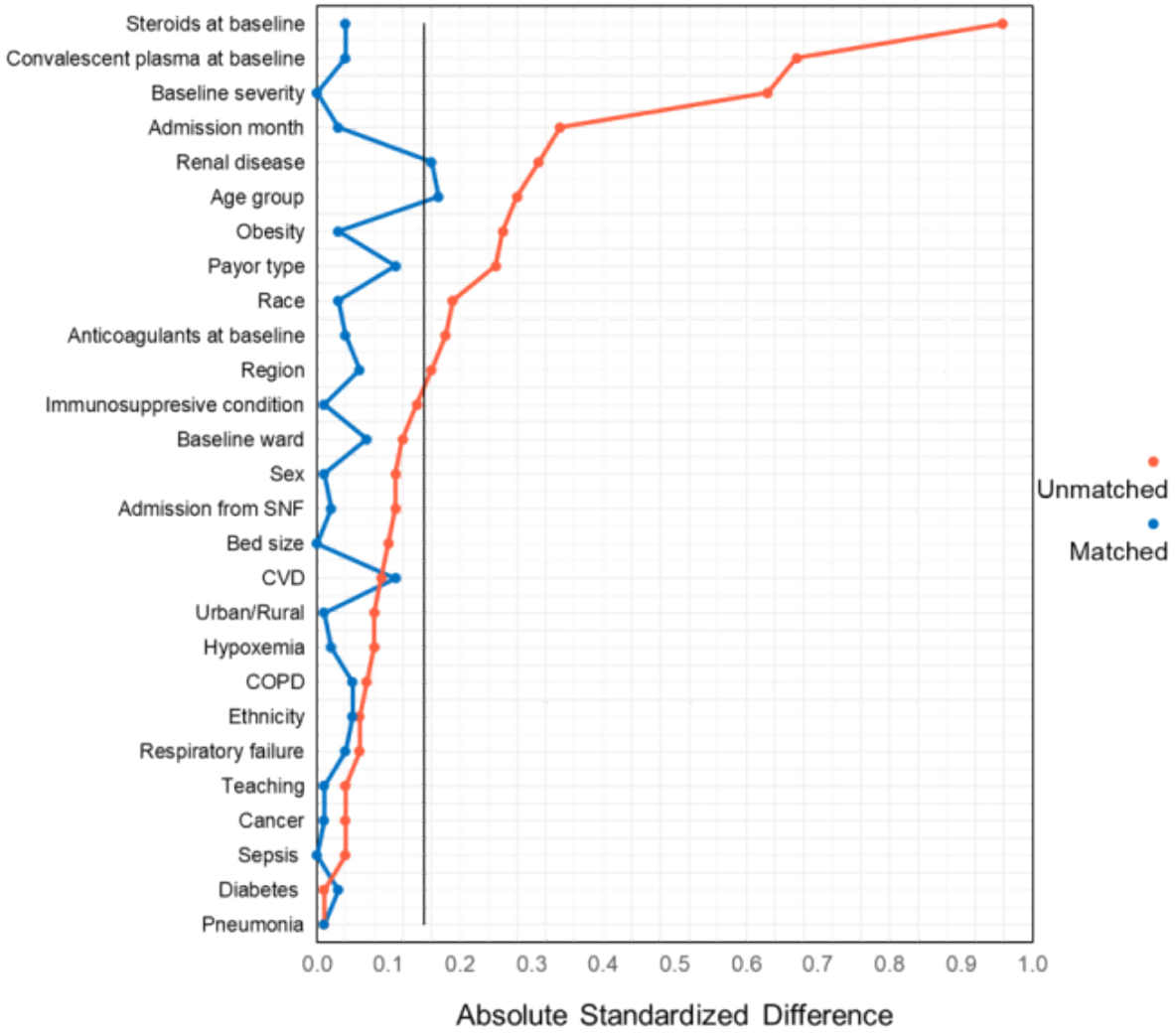
Matching with replacement was conducted: allowed for most of the patients treated with RDV to be matched despite the restrictive matching criteria



Preferential within-hospital matching with replacement



Statistical Analysis: Baseline check/diagnostics



- The balance was verified by the absolute standardized differences of the covariates included in the model to estimate the propensity score.
- All covariates, except age group and renal disease, had an absolute standardized difference value of <0.15
  - Any covariates with absolute standardized difference of >0.15 were adjusted for in outcomes assessment, in addition to adjusting for other baseline and clinical covariates

Statistical Analysis: Outcome assessment

Time to mortality outcome: Cox Proportional Hazards Model

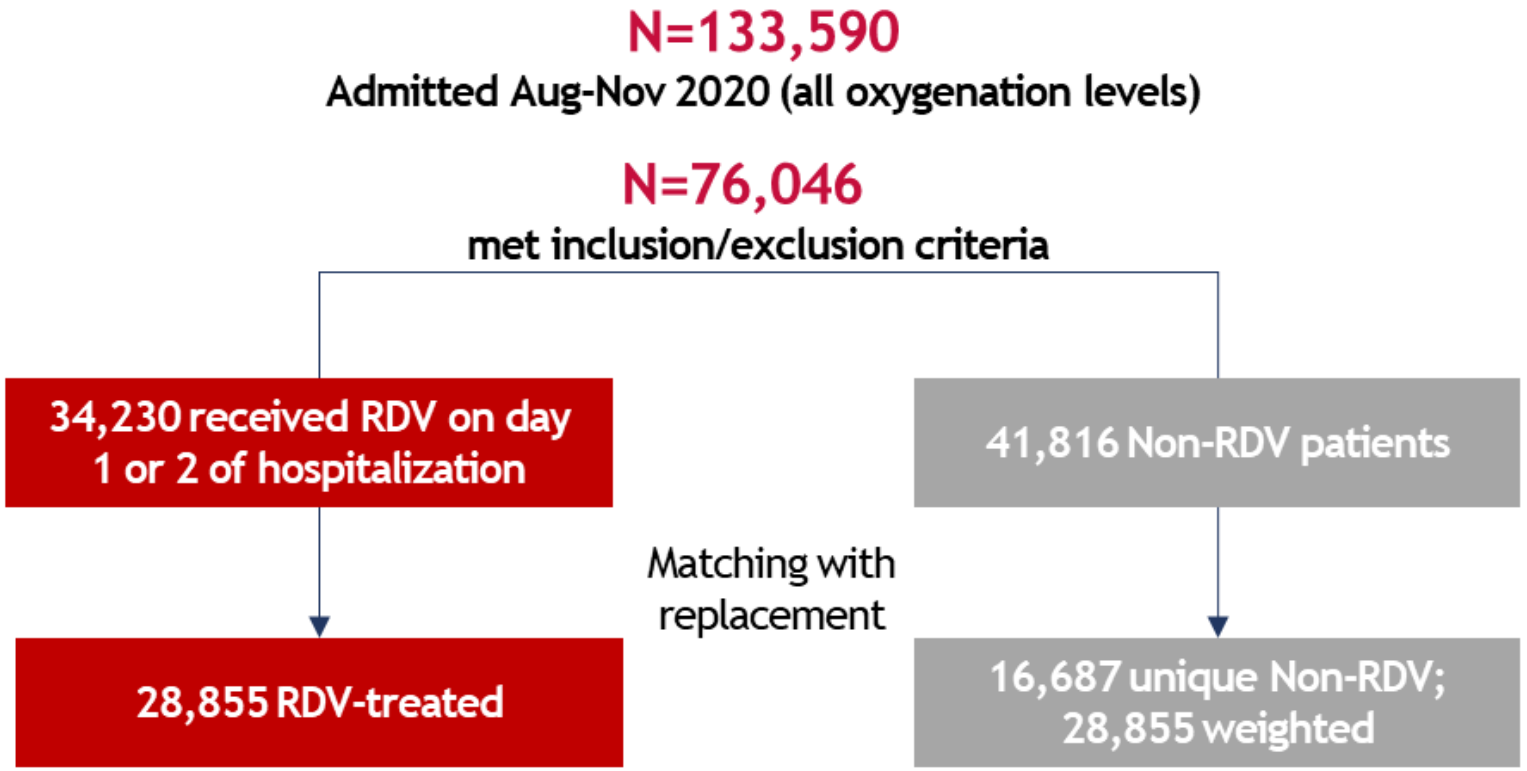
- **Mortality:** discharge status of “expired” or “hospice”
- **Event of interest:** Time to 14-day and 28-day mortality after baseline period
- **Healthy discharge:** patients who were discharged before the 14-day or 28-day time period were censored at the 14-day and 28-day time points
- A marginal model to account for hospital-level cluster effects was used

The following variables were adjusted for in the outcomes analyses models:

- Age (continuous)
- Admission month
- Anticoagulants use at baseline
- Convalescent plasma at baseline
- Steroids use at baseline
- Tocilizumab use at baseline
- DVT/PE in discharge diagnosis
- Ischemic stroke in discharge diagnosis
- Baseline stay (general ward vs. step-down unit vs. ICU)
- Covariates with standardized difference absolute value >0.15 after matching

Results

Study population



Demographic and hospital characteristics after matching

		RDV cohort	Non-RDV cohort
# of Patients		**n=28855**	**n=28855**
Age group	18-34	4%	2%
	35-49	13%	11%
	50-64	31%	29%
	65+	53%	58%
Gender	Male	56%	55%
Race	White	73%	74%
	Black	13%	13%
	Other	14%	14%
Obesity		41%	40%
COPD		27%	29%
Cardiovascular disease		79%	83%
Diabetes		43%	44%
Renal disease		17%	24%
Cancer		4%	4%

		RDV cohort	Non-RDV cohort
# of Patients		**n=28855**	**n=28855**
Admission month	Aug	16%	17%
	Sep	14%	13%
	Oct	26%	27%
	Nov	44%	44%
Bed size	0-199	20%	20%
	200-499	50%	50%
	500+	29%	29%
Rural/urban	Urban	84%	85%
Teaching	Yes	43%	43%
Region	Midwest	30%	32%
	Northeast	6%	6%
	South	53%	50%
	West	12%	12%
Hospital ward at baseline	General ward	73%	70%
	Step-down	7%	7%
	ICU	20%	24%

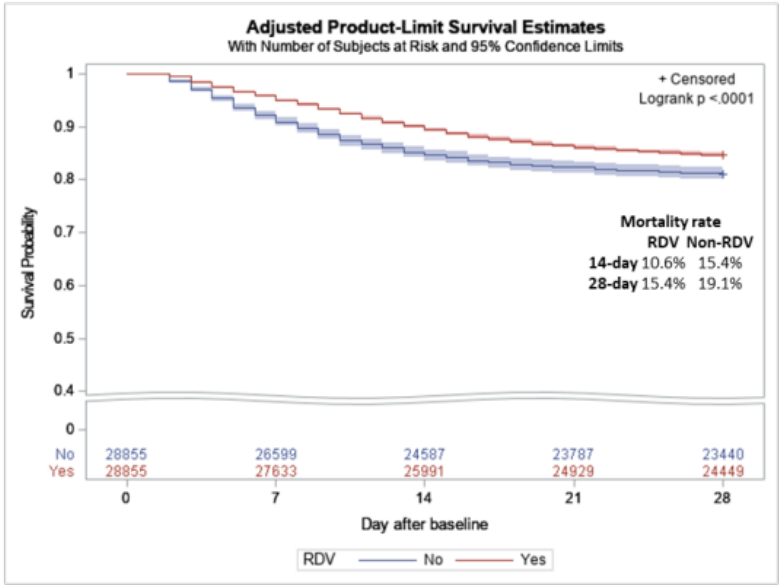
Other patient characteristics after matching

		RDV cohort	Non-RDV cohort
# of Patients		**n=28855**	**n=28855**
Ethnicity	Hispanic	17%	16%
	Non-Hispanic	72%	74%
	Unknown	11%	10%
Primary payor	Commercial	29%	25%
	Medicare	54%	59%
	Medicaid	8%	8%
	Other	9%	8%
Admission source - SNF		2%	3%

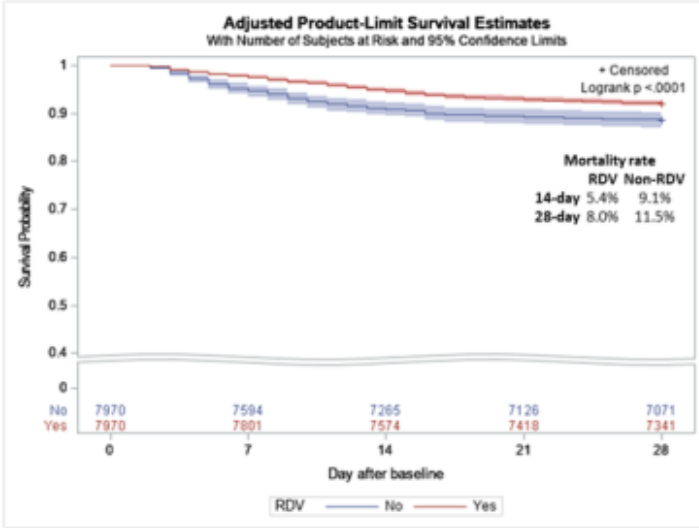
	RDV cohort	Non-RDV cohort
# of Patients	**n=28855**	**n=28855**
Immunosuppressive condition	4%	4%
Sepsis in admit diagnosis	7%	7%
Respiratory failure in admit diagnosis	3%	3%
Hypoxemia in admit diagnosis	2%	2%
Pneumonia in admit diagnosis	2%	2%
Anticoagulants at baseline	15%	16%
Corticosteroids at baseline	96%	97%
Convalescent plasma at baseline	32%	33%

Kaplan-Meier curves for time to mortality

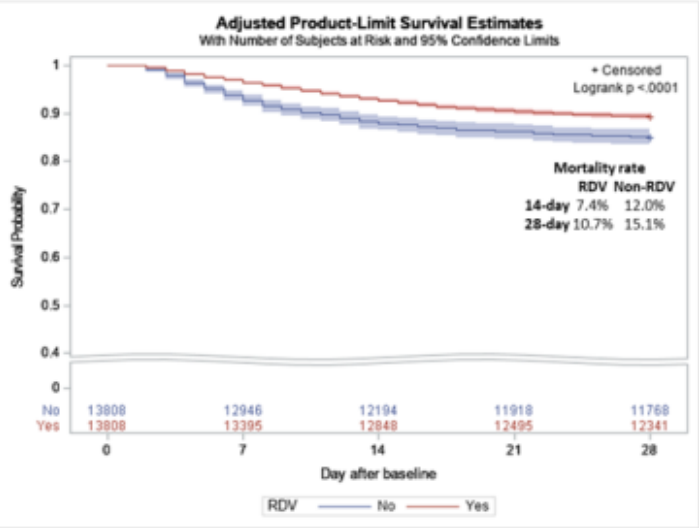
A. Overall



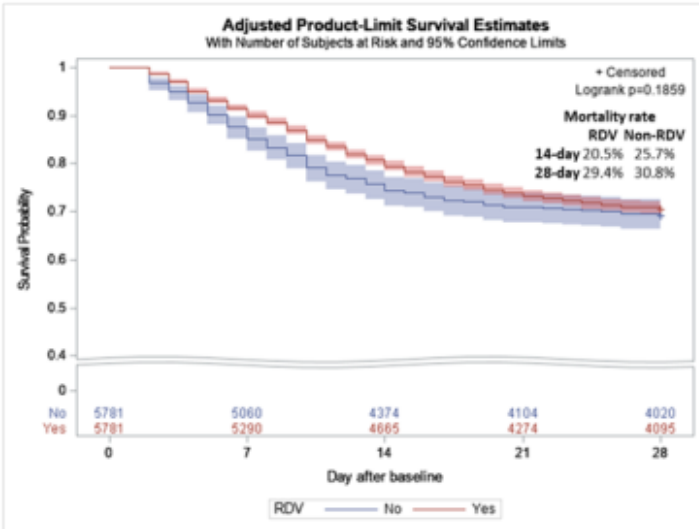
B. No supplementary oxygen



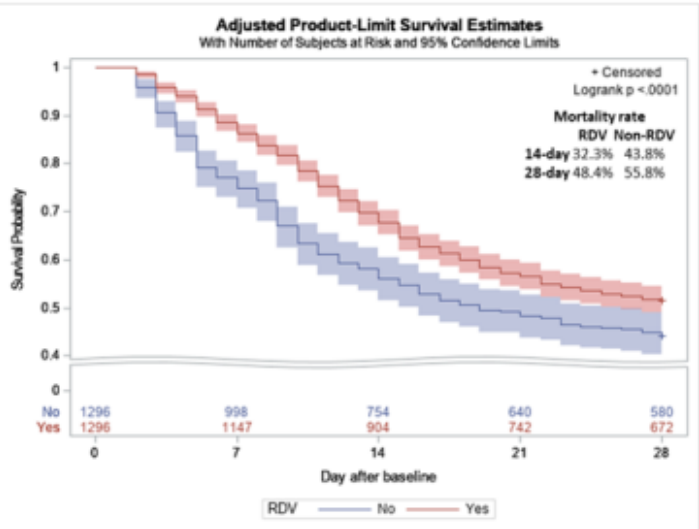
C. Low-flow oxygen



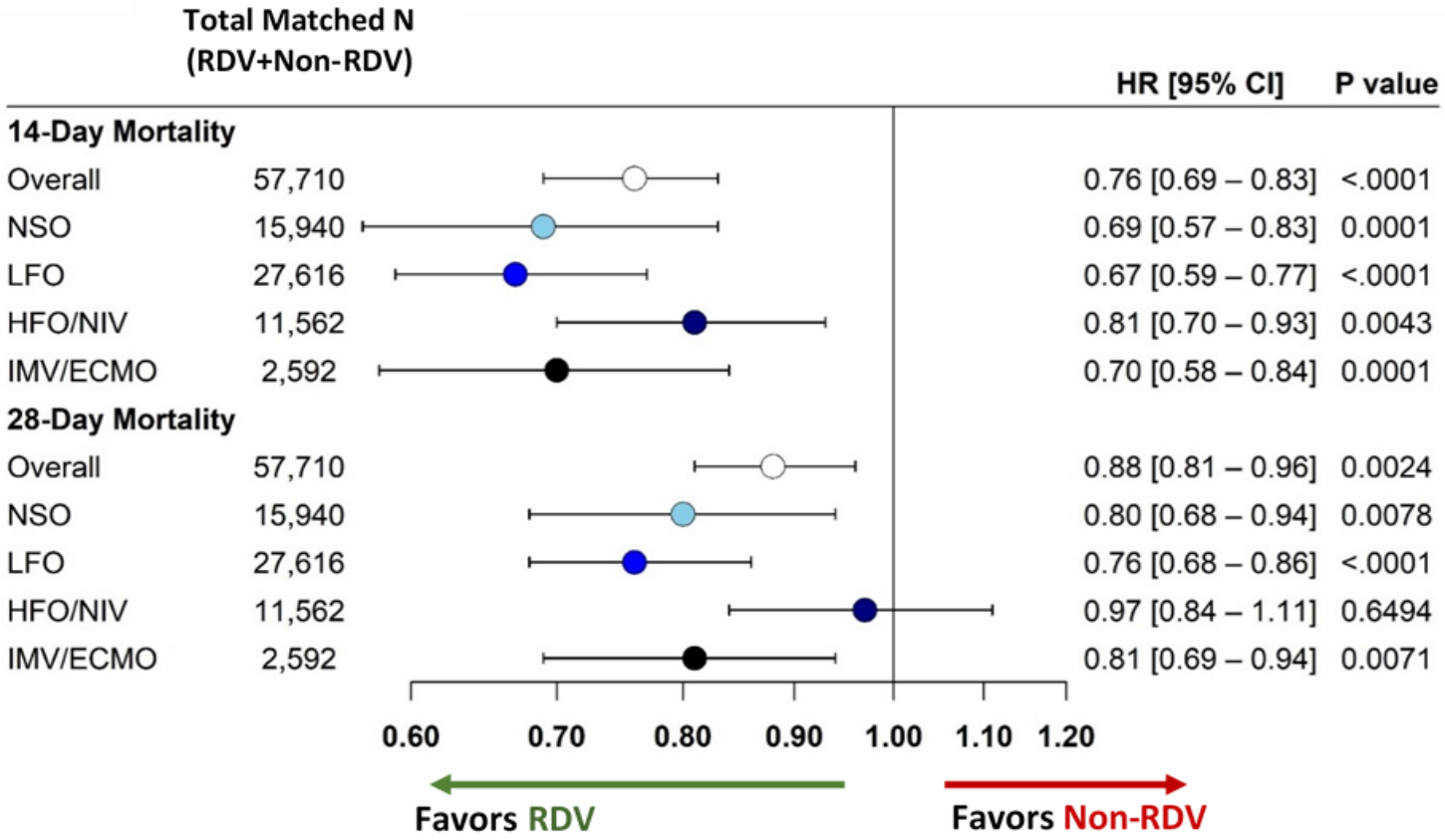
D. High-flow oxygen/NIV



E. IMV/ECMO



Patients treated with RDV had a significantly lower risk of mortality at 14- and 28-days



NSO: no supplementary oxygen, LFO: low-flow oxygen, HFO/NIV: high-flow oxygen/non-invasive ventilation, IMV/ECMO: invasive mechanical ventilation/ECMO

** Adjusted for hospital-level random effects and age, admission month, anticoagulants use at baseline, convalescent plasma at baseline, corticosteroids use at baseline, tocilizumab use at baseline, ICU stay/Step-down/General ward at baseline and other covariates with absolute standardized difference>0.15*

Conclusions

- In this large retrospective comparative effectiveness study of adults hospitalized with COVID-19 in the US, initiation of RDV upon hospital admission was associated with a significant reduction in mortality.
  - These benefits were most apparent among patients receiving NSO, LFO or IMV/ECMO at baseline.

- These data support the initiation of RDV immediately after hospitalization for COVID-19.

- This study contributes to the growing body of evidence indicating that RDV is associated with improved survival outcomes for hospitalized COVID-19 patients.