Remdesivir is associated with decreased mortality in hospitalised COVID-19 patients requiring high-flow oxygen in the United States

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Key Findings

- In routine clinical practice setting, **remdesivir is associated with reduced mortality** regardless of supplemental oxygen requirements upon admission
- This clear and consistent benefit was observed across **all dominant variant periods** from December 2020 to April 2022

Objective of the study

— To compare inpatient all-cause mortality in patients who were administered remdesivir (RDV) in the first two days of hospitalization to patients vs. those not administered remdesivir during hospitalization among patients hospitalized **with COVID-19 as a primary discharge diagnosis and receiving high-flow oxygen/non-invasive ventilation upon admission**

  - Endpoints were examined according to timing of COVID-19 hospitalization in **different variants of concern (VOC) periods:** pre-Delta (December 2020-April 2021), Delta (May 2021-November 2021) and Omicron (December 2021- April 2022)
  - Endpoints were also examined among patients receiving **no supplementary oxygen, low-flow oxygen and invasive mechanical ventilation/ECMO upon admission**

— **Primary endpoints:**

  - 14-day in-hospital mortality
  - 28-day in-hospital mortality

Study Design

Comparative effectiveness study using PINC AI Healthcare Database

— Data source: hospital billing database covering ~25% of all US hospitalizations from 48 states

— All baseline variables are examined within the first two days of hospitalization

Inclusion criteria	✓	First admission to the hospital Dec 1, 2020-Apr 30, 2022
	✓	Age ≥18 years old
	✓	***Primary*** **discharge diagnosis of COVID-19** (ICD-10-CM: U07.1) flagged as "present-on-admission"
Exclusion criteria	✗	Pregnant
	✗	Had incomplete /erroneous data fields
	✗	Transferred from another hospital or hospice
	✗	Transferred to another hospital
	✗	Admitted for elective procedures
	✗	Discharged or died during the baseline period (first two days of hospitalization)

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

— **Primary Endpoints:** 14-day and 28-day all-cause inpatient mortality (discharge status of "expired" or "hospice")

— **VOC periods:** Pre-Delta (Dec 2020-Apr 2021), Delta (May-Nov 2021), Omicron (Dec 2021-Apr 2022)

Methodology published previously in peer-reviewed journals

Clinical Infectious Diseases

MAJOR ARTICLE

Remdesivir Treatment in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19): A Comparative Analysis of In-hospital All-cause Mortality in a Large Multicenter Observational Cohort

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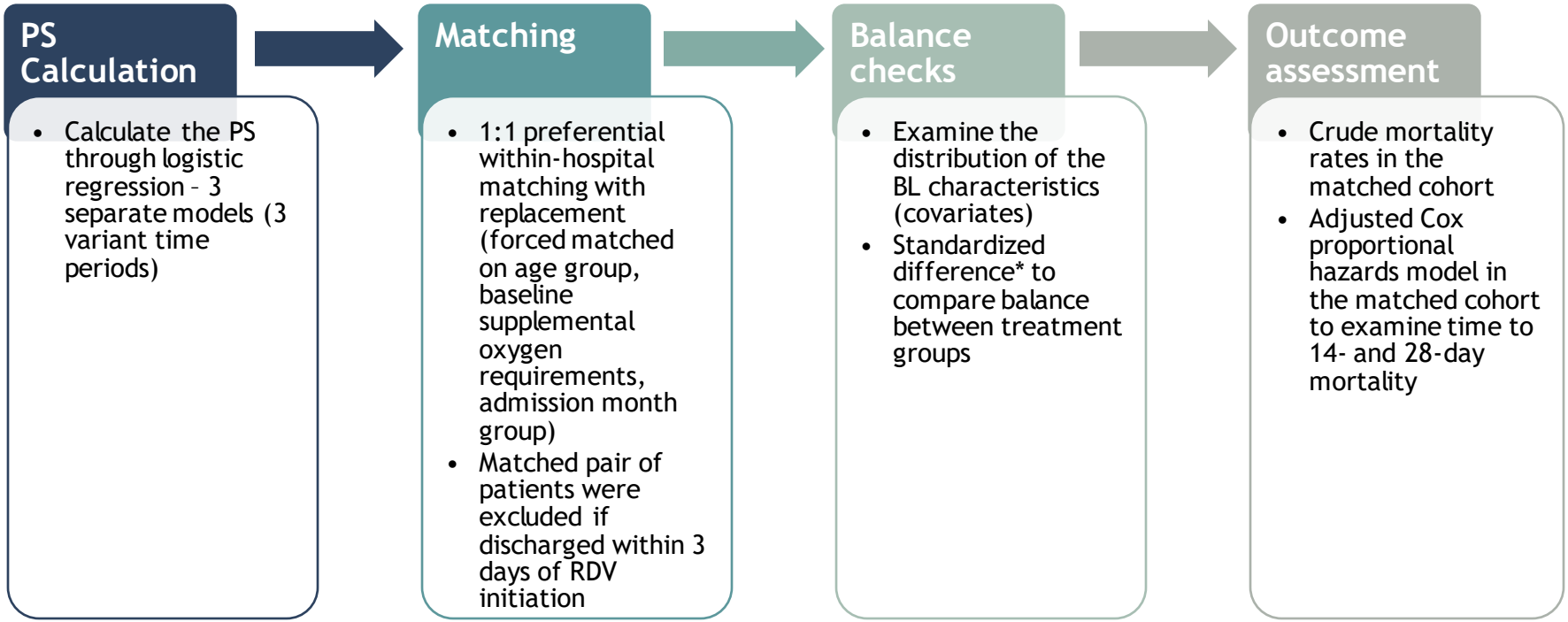
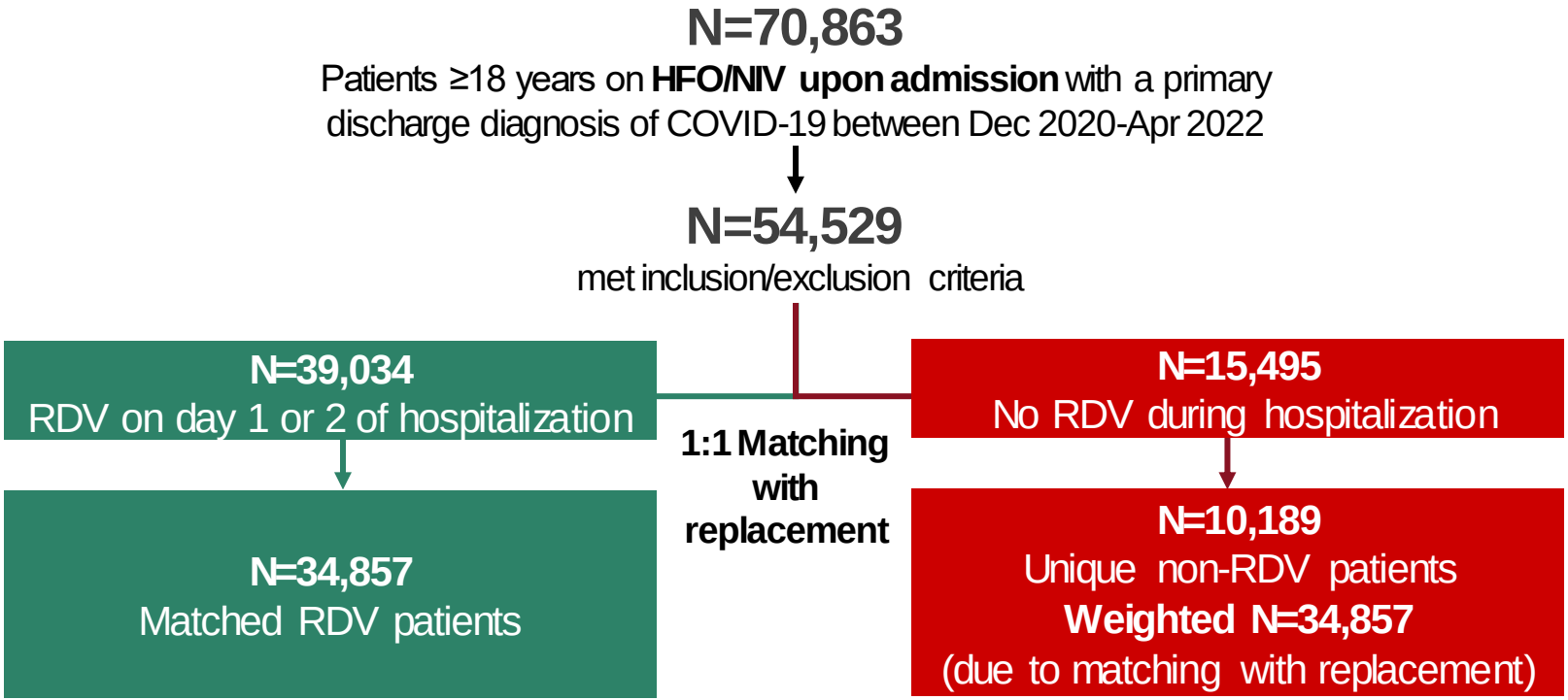
Statistical analysis approach

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



BL: baseline; PS: propensity score; RDV: remdesivir; NSOc: No supplementary oxygen charges; LFO: Low Flow Oxygen; HFO/NIV: High Flow Oxygen; IMV/ECMO: Invasive Mechanical Ventilation / Extracorporeal Membrane Oxygenation
*Standardized difference is the difference in mean (mean RDV – mean control) divided by the standard deviation of the groups

Study cohort

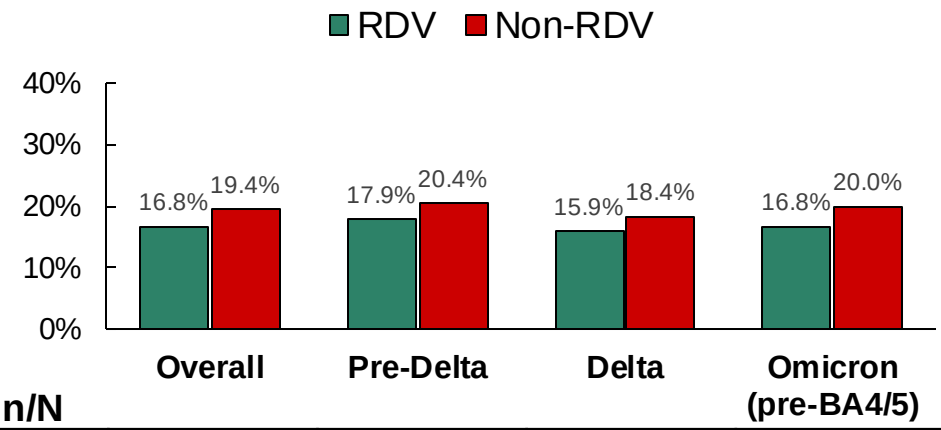


Since matching with replacement technique was used, 1 non-RDV patient could be matched multiple times to different RDV patients

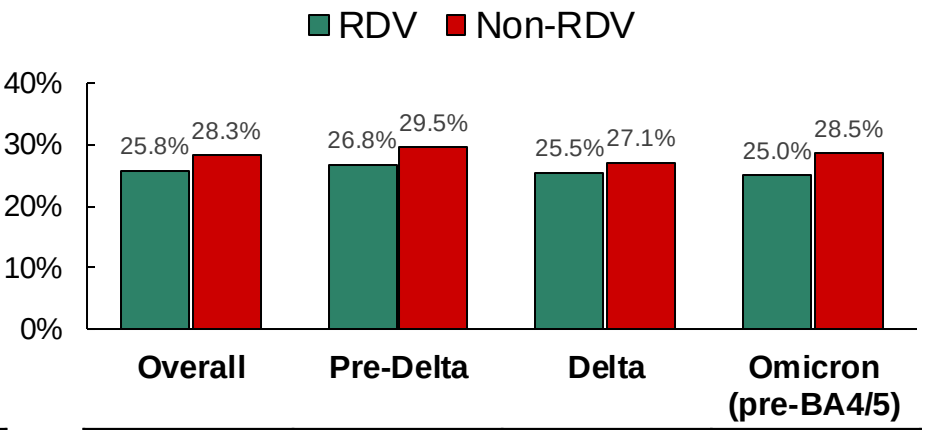
Unadjusted analysis

Among patients on HFO/NIV upon admission, mortality rates were significantly lower for RDV vs. non-RDV across all variant periods

14-day mortality



28-day mortality

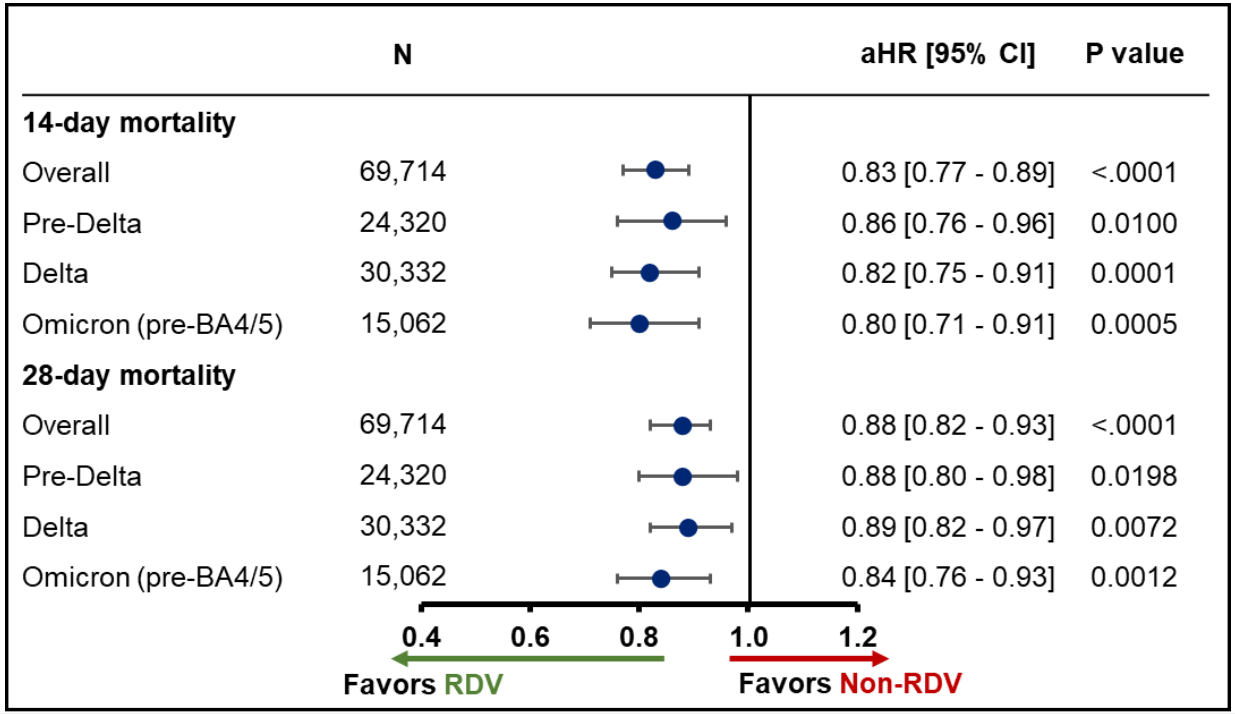


n/N	Overall	Pre-Delta	Delta	Omicron (pre-BA4/5)
RDV	5853/34857	2180/12160	2409/15166	1264/7531
Non-RDV	6770/34857	2478/12160	2783/15166	1509/7531

Overall	Pre-Delta	Delta	Omicron (pre-BA4/5)
9009/34857	3260/12160	3863/15166	1886/7531
9853/34857	3591/12160	4115/15166	2147/7531

Adjusted analysis

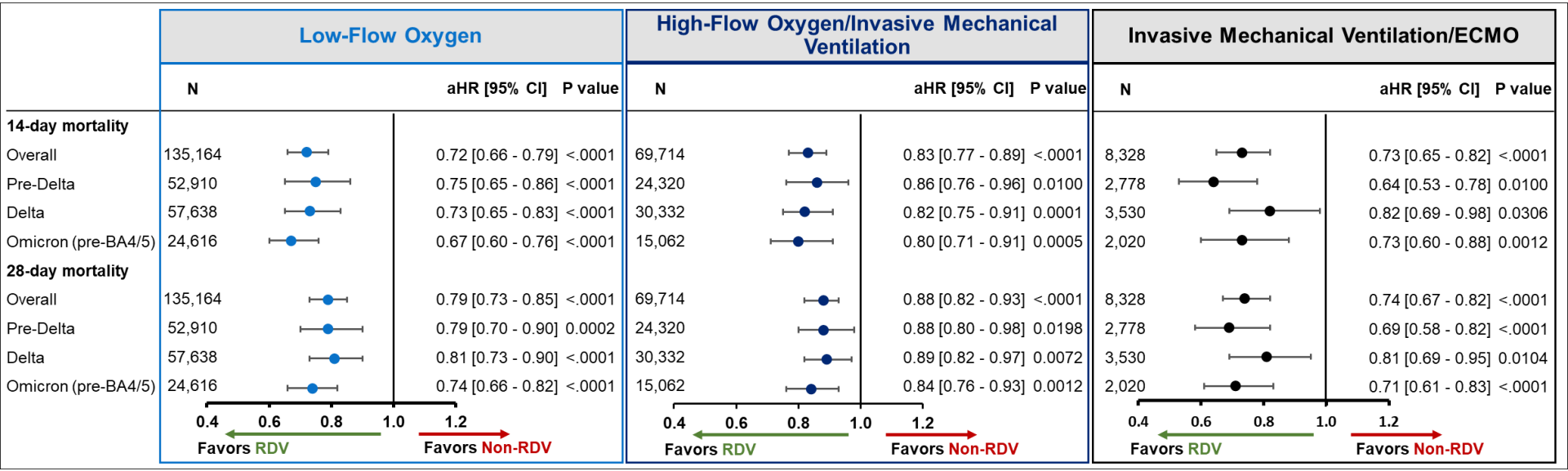
Among patients on HFO/NIV upon admission, RDV had significantly lower mortality risk compared to non-RDV across all VOC periods



Note: Estimates adjusted for age, admission month, admission venue (ICU vs. general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab)

Adjusted analysis

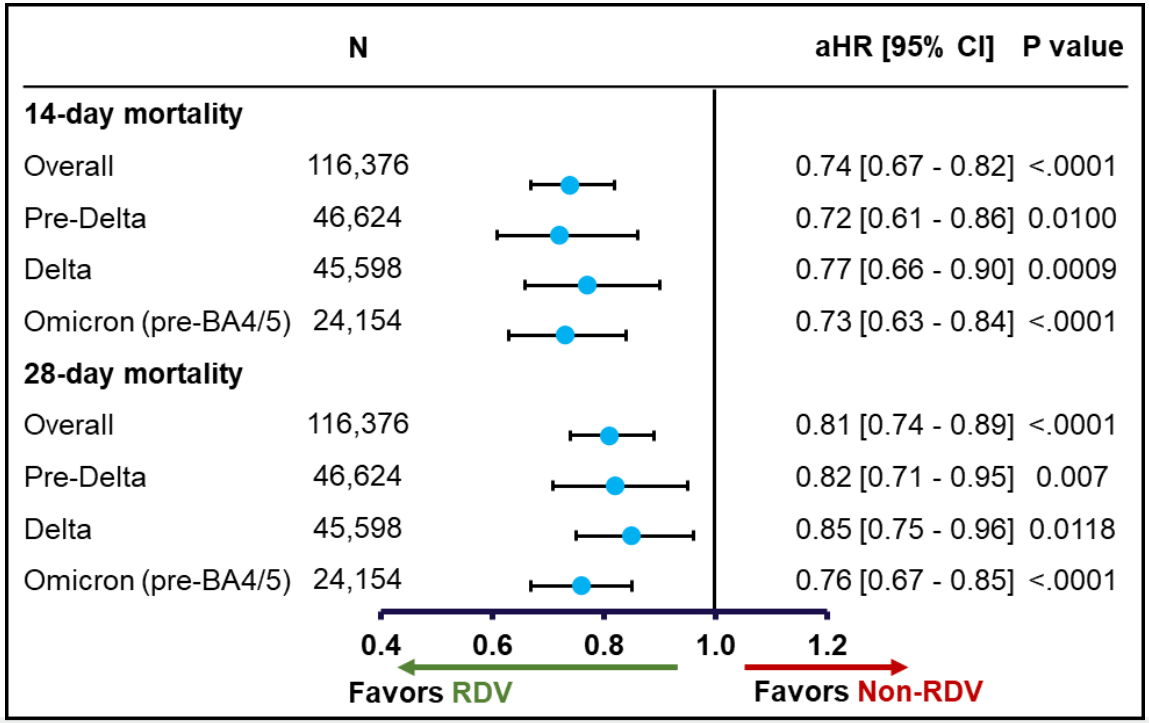
Consistent mortality reduction with RDV observed for all levels of supplemental oxygenation requirements across all VOC periods



Note: Estimates adjusted for age, admission month, admission venue (ICU vs. general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab)

Adjusted analysis

RDV also showed a consistent benefit among patients not reporting supplementary oxygen upon admission



Note: Estimates adjusted for age, admission month, admission venue (ICU vs. general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab)

Conclusions

- Using a large cohort of hospitalized COVID-19 patients in routine clinical practice, this study demonstrated that the **initiation of RDV upon admission leads to statistically significant reduction in mortality** across all variant periods studied (through April 2022)
- Given the **high mortality rates in severely or critically ill COVID-19 patients** across emerging variants, **use of remdesivir in this population could be life-saving**
- While the initiation of antivirals early in the disease course is clearly optimal to decrease risk of inflammatory dysregulation, there are still benefits of reduction in mortality **when initiated in patients presenting later in the disease course**

Questions?

Statistical Analysis: PS calculation

PS calculation → Matching → Baseline check/diagnostics → Outcome assessment

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, region of the hospital
- **Admission month**
- **Admission from SNF**
- **ICU/General ward** at baseline
- **Severity level** 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: corticosteroids, convalescent plasma, anticoagulants, tocilizumab, baricitinib

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

Statistical Analysis: Matching

PS calculation → **Matching** → Baseline check/diagnostics → Outcome assessment

1:1 Preferential Same-Hospital Matching with replacement

1. PS-matching (caliper=0.2x s.d. of the logit of the PS) for patients with same age group, same supplemental oxygenation, same two/three-month blocks of admission month within the same hospital

If unmatched in step 1

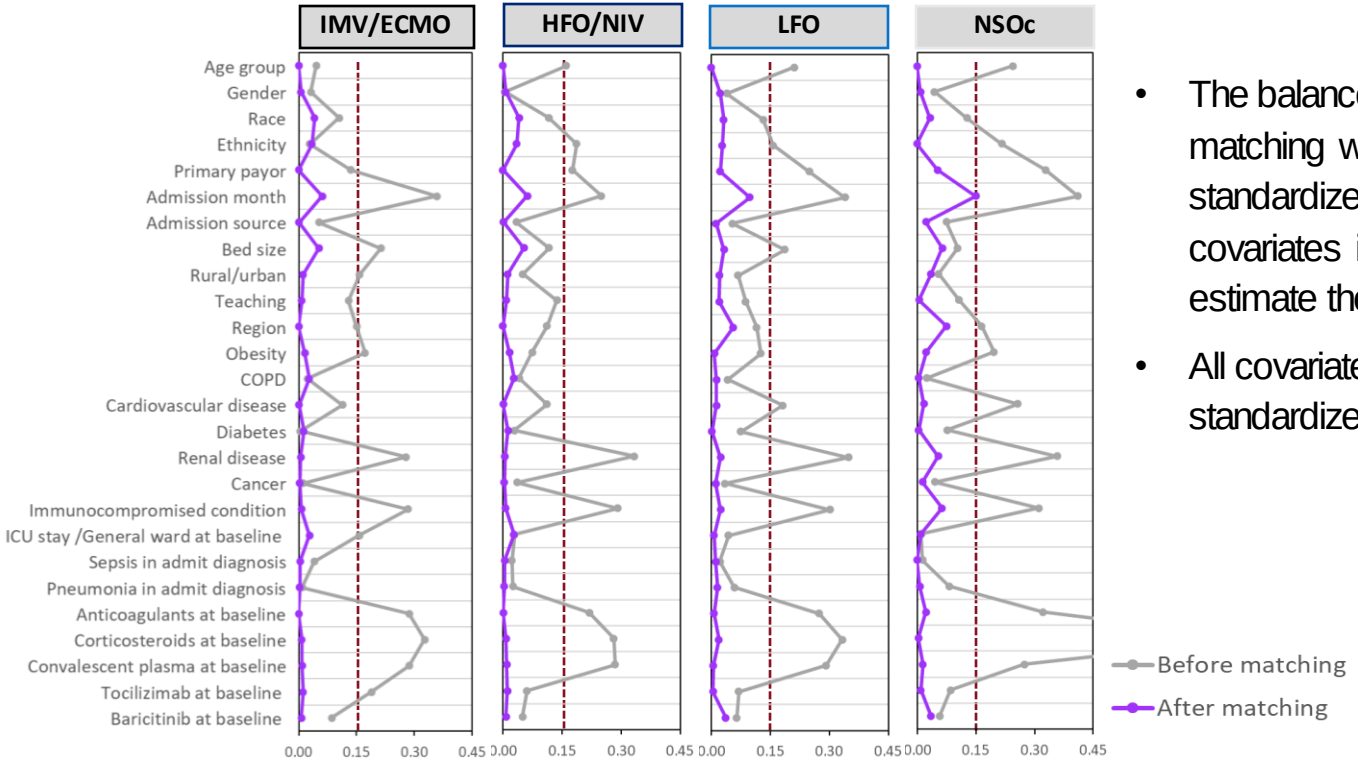
2. PS-matching (caliper=0.2x s.d. of the logit of the PS) for patients with same age group, same supplemental oxygenation, same two/three-month blocks of admission month within another RDV-using hospital of same bed size

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

Matching with replacement: allowed for majority of the patients treated with RDV to be matched and included in the analysis despite a restricted matching criteria and higher % of RDV use in the study cohort; hence conclusions made are applicable to majority of the RDV patients

Statistical Analysis: Baseline check/diagnostics

PS calculation → Matching → Baseline check/diagnostics → Outcome assessment



- The balance in the covariates after matching was verified by the absolute standardized differences of the covariates included in the model to estimate the propensity scores
- All covariates had an absolute standardized difference value of <0.15

Statistical Analysis: Outcome assessment

PS calculation → Matching → Baseline check/diagnostics → 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
  - Baricitinib at baseline
  - Hospital ward upon admission (general ward vs. ICU unit)