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Convalescent Plasma Therapy and Mortality among US Veterans Hospitalized with Non-Severe COVID-19: An Observational Analysis Emulating a Target Trial

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Disclosures

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Background

- Convalescent plasma (CP) widely used to treat coronavirus disease 2019 (COVID-19), but effectiveness remains unclear
- CP of donors who recovered from COVID-19 contains antiviral and anti-inflammatory components with potential to provide immunity to recipients
- CP expected to be most effective during first week of infection

Most **RCTs** were small and reported imprecise and inconclusive effect estimates for mortality

Effect Estimate (95% CI)	N	Authors	Location
0.50 (0.09, 2.65)	160	Libster et al.	Argentina
1.04 (0.66, 1.63)	464	Agarwal et al.	India
1.00 (0.93, 1.07)	11,558	RECOVERY collaborative group	United Kingdom
0.79 (0.52, 1.19)	4 studies	Wang et al.	Meta-Analysis
0.58 (0.29, 1.15)	5 studies	Klassen et al.	Meta-Analysis

Most **observational studies** showed a lower mortality risk in patients treated with CP

Effect Estimate (95% CI)	N	Authors	Location
0.17 (0.03, 1.11)*	387	Salazar et al.	United States
0.59 (0.53, 0.66)	11 studies	Wang et al.	Meta-Analysis
0.50 (0.37, 0.67)	13 studies	Klassen et al.	Meta-Analysis

*Transfused within 72 hours after hospital admission

Objective

To determine if early treatment with convalescent plasma reduces 30-day mortality among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive Veterans hospitalized at a Department of Veterans Affairs (VA) medical center with non-severe disease.

Target Trial

- A hypothetical pragmatic trial that we would have liked to conduct
- Observational data used to emulate target trial

Summary Results: 30-day Mortality

	Convalescent Plasma group (N=402)	Non-Convalescent Plasma group (N=10,867)
Number of deaths (unique deaths)	40 (40)	671 (343)
Unadjusted risk (95% CI)	9.9% (7.1, 13.2)	6.1% (5.5, 6.9)
IP* weighted risk (95% CI)	6.5% (4.0, 9.7)	6.2% (5.6, 7.0)

	Risk Difference (95% CI)	Hazard Ratio (95% CI)
Unadjusted	3.76% (0.91, 6.94)	1.64 (1.14, 2.18)
IP* weighted	0.30% (-2.30, 3.60)	1.04 (0.64, 1.62)

*Inverse probability

Specification and Emulation of target trial

Eligibility Criteria

Target Trial Specification	Target Trial Emulation
• US Veterans aged 21-80 years old	• Same as target trial
• Hospitalized between May 1, 2020 and November 17, 2020 with a positive SARS-CoV-2 test at a VA Medical Center where convalescent plasma had been administered to at least one patient and remained a current practice at that medical center	• Eligibility criteria assessed using data from VA EMR (ICD-9 and ICD-10 diagnosis codes, ICD-10 and CPT procedure codes, vital sign recordings, laboratory data, pharmacy documentation)
• A positive SARS-CoV-2 test within 7 days before or after hospital admission	
• No prior treatment with convalescent plasma	
• No long-term care in a domiciliary or nursing home in the past 90 days	
• **Minimum oxygen saturation (measured within the past day) >=90%**	
• **No prior intubation, ventilation, high flow oxygen, extracorporeal membrane oxygenation, dialysis, or vasopressors during current hospitalization**	
• Vitals (pulse, respiration, temperature, systolic blood pressure) and acute labs (hemoglobin, platelet, white blood cells) measured within the past 2 days	
• Albumin, Alanine Aminotransferase (ALT), creatinine measured within the past 30 days	
• Weight measurement recorded in the past 2 years	

Specification and Emulation of target trial

Protocol Component	Target Trial Specification	Target Trial emulation
Treatment Strategy	• Receipt of convalescent plasma transfusion • No receipt of convalescent plasma transfusion	Same as target trial
Outcome	30-day mortality	Same as target trial
Follow-Up	• Starts at treatment date (within 2 days after both hospitalization and SARS-CoV-2 positive test) • Ends at 30 days or death	Same as target trial

Specification and Emulation of target trial

Protocol Component	Target Trial Specification	Target Trial emulation
Treatment Assignment	Individuals are randomly assigned to a treatment strategy. Individuals and treating physicians are aware of assigned treatment.	Classified patients according to treatment with which their data were compatible and attempted to emulate randomization by adjusting for baseline covariates through inverse probability (IP) weighting
Causal Contrast	• Intention-to-treat effect • Per-protocol effect	• Observational analogue of per-protocol effect

Baseline Covariates in Inverse Probability Weights

- Age
- Sex
- Race
- Ethnicity
- Region
- Body Mass Index
- Smoking Status
- Cardiovascular disorder within past 5 years
- COPD*
- Dementia*
- Diabetes*
- Hypertension*
- eGFR within past 30 days
- Intensive Care Unit Admission[+]
- Glucocorticoid use[+]
- Remdesivir use[+]
- Supplemental (non-high flow) oxygen[+]
- Minimum oxygen saturation in the past day[+]
- First oxygen saturation during hospitalization[+]
- Maximum white blood cell count within past 2 days[+]
- Systemic Inflammatory Response Syndrome
- Calendar day of Trial Start
- Trial start day relative to time of hospitalization and positive SARS-CoV-2 test

*Within past 2 years

[+] During COVID hospitalization prior to trial start

Repeated eligibility for target trial emulation

i – **trial id**	t_0 – **time since hospitalized with positive SARS-CoV-2 test**	e – **eligibility**	**z** – **treatment**	Y – **outcome**	t_m^* – **maximum follow-up time**
Bob.1	0	1	0	1	20
Bob.2	1	1	1	1	19
Bob.3	2	0	1	1	18
Sue.1	0	1	0	0	30
Sue.2	1	1	0	0	30
Sue.3	2	1	0	0	30

Note: These are not real patient data.

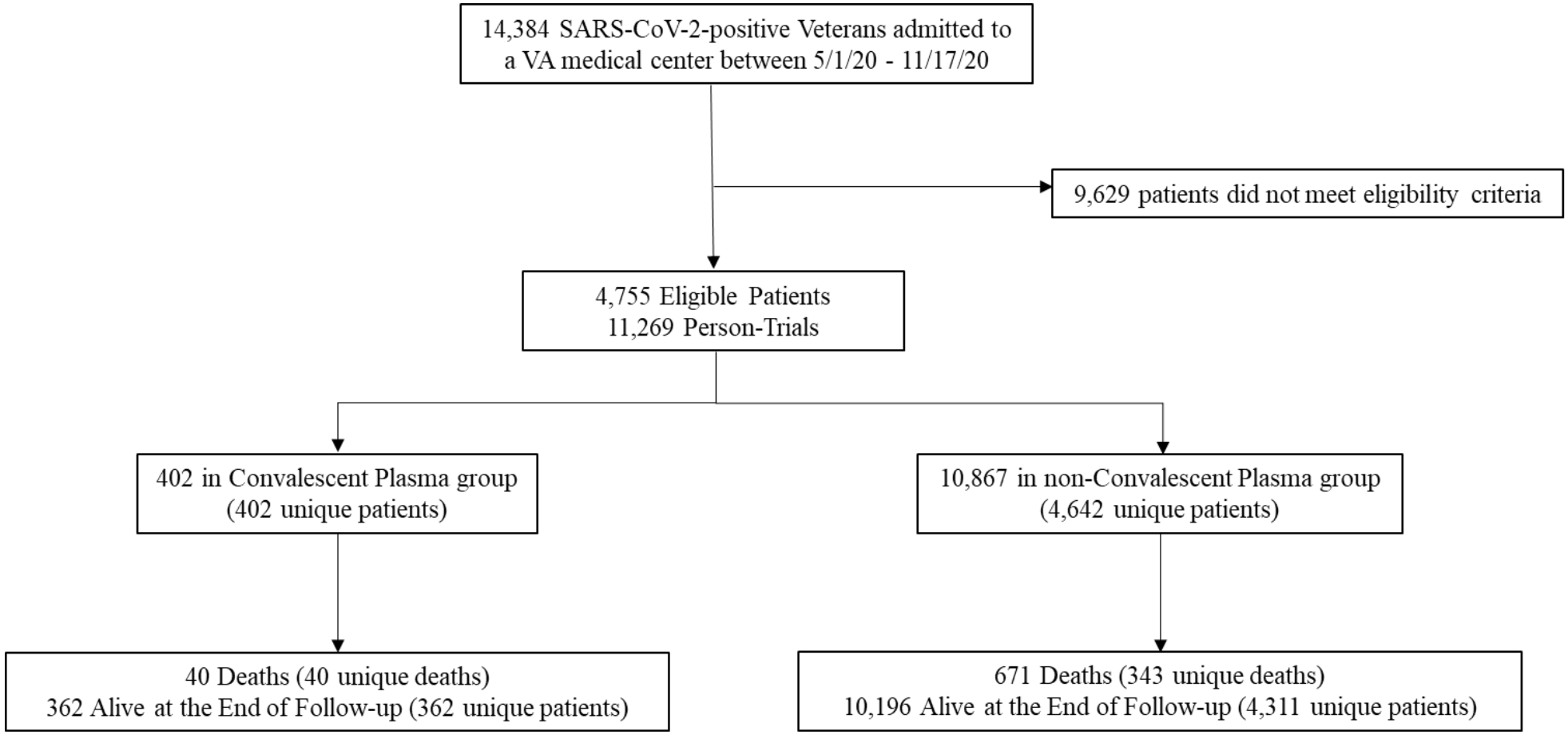
Statistical analysis for target trial emulation

- Estimated the incidence of mortality using a weighted pooled logistic regression model:

$$logit(p_{Time\ =t}) = \left(\beta_0 + \beta_1 Treatment + \boldsymbol{\beta_2}\, sp(Time) + \boldsymbol{\beta_3} Treatment * sp(Time)\right)$$

- Adjusted for 23 *a priori* baseline prognostic factors via inverse probability weighting
- Nonparametric bootstrapping (B=1500) to calculate confidence intervals

Flow chart for selection of eligible patients



Baseline Characteristics

Characteristic, mean (standard deviation) or n (%)	Convalescent Plasma group (N=402)	Non-Convalescent Plasma group (N=10,867)
Age	65.0 (11.3)	64.1 (12.0)
Sex, male	370 (92)	10,101 (93)
Race		
White	258 (64)	6,194 (57)
Black	109 (27)	3,814 (35)
Other	35 (9)	859 (9)
Ethnicity, Hispanic or Latino	52 (13)	1123 (10)
Region		
Central	114 (28)	2,584 (24)
Northeast	69 (17)	2,367 (22)
Pacific	27 (7)	1,527 (14)
Southeast	192 (48)	4,389 (40)
Body Mass Index (kg/m^2)	32.2 (7.1)	31.0 (7.2)
Current Smoker	81 (20)	2,836 (26)
Cardiovascular Disorder within the past 5 years	156 (39)	4,663 (43)
Chronic Obstructive Pulmonary Disease *	119 (30)	2,463 (23)
Dementia *	29 (7)	816 (8)
Diabetes *	219 (55)	5,145 (47)
Hypertension *	307 (76)	7,747 (71)

Note: Each individual patient may contribute to multiple target trials

*Within past 2 years

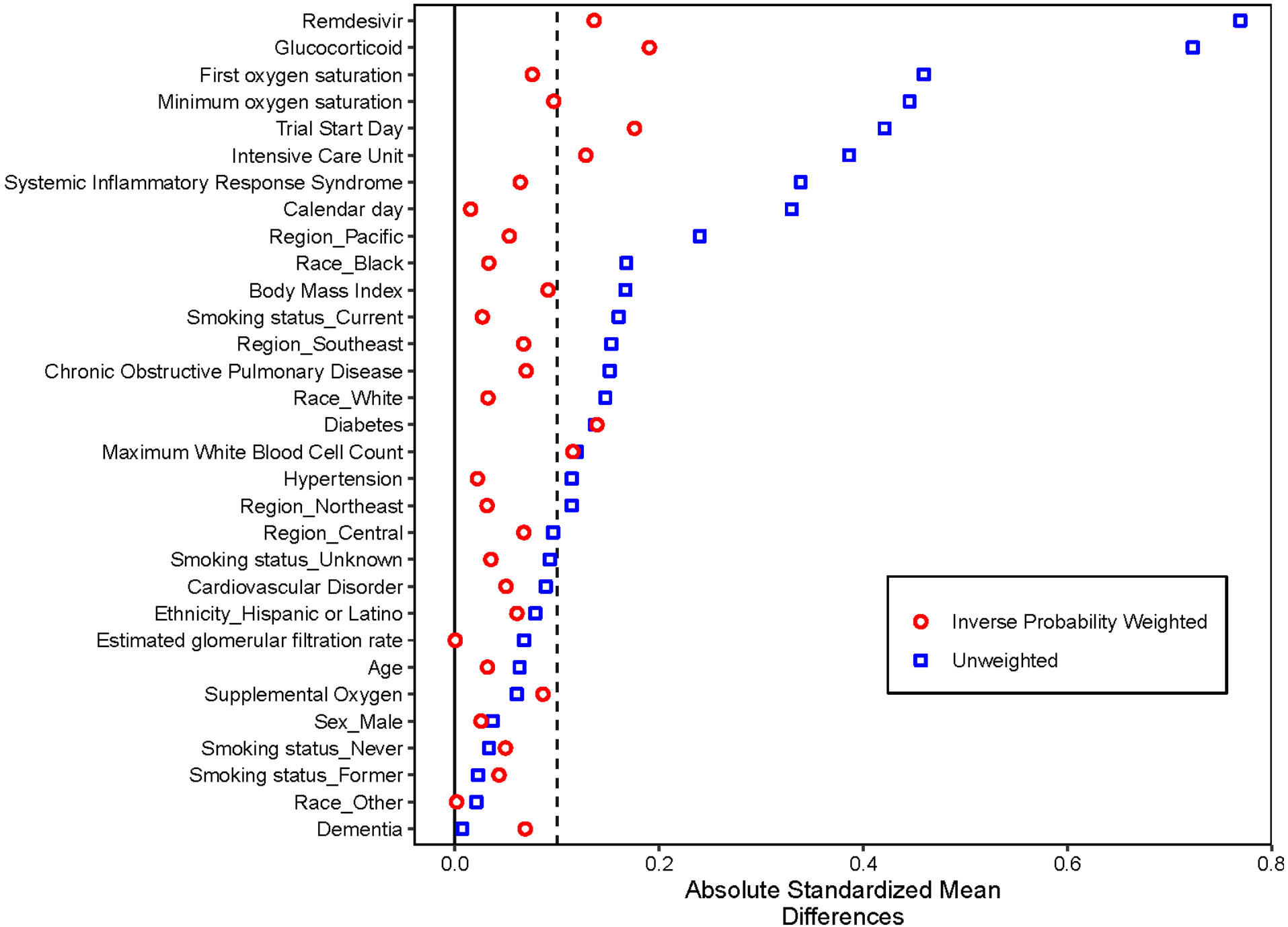
Baseline Characteristics, continued

Characteristic, mean (standard deviation) or n (%)	Convalescent Plasma group (N=402)	Non-Convalescent Plasma group (N=10,867)
Estimated glomerular filtration rate (mL/min/1.73m^2) within the past 30 days [+]	79.3 (59.1, 94.8)	77.3 (54.9, 93.6)
In Intensive Care Unit [§]	153 (38)	2,204 (20)
Glucocorticoid use [§]	215 (54)	2,258 (21)
Remdesivir use [§]	187 (47)	1,476 (14)
Supplemental (non-high flow) oxygen [§]	9 (2)	161 (2)
Minimum oxygen saturation in the past day [§]	93.3 (2.8)	94.6 (3.1)
First oxygen saturation during hospitalization [§]	93.8 (3.8)	95.5 (3.3)
Maximum White Blood Cell count (1000 cells/μL) in past 2 days [+, §]	6.6 (4.6, 9.0)	5.9 (4.5, 8.1)
Systemic Inflammatory Response Syndrome [§]	243 (60)	4,739 (44)
Calendar day of Trial Start	249 (52)	231 (52)

Note: Each individual patient may contribute to multiple target trials

[+] Median and interquartile range presented due to non-normal distribution

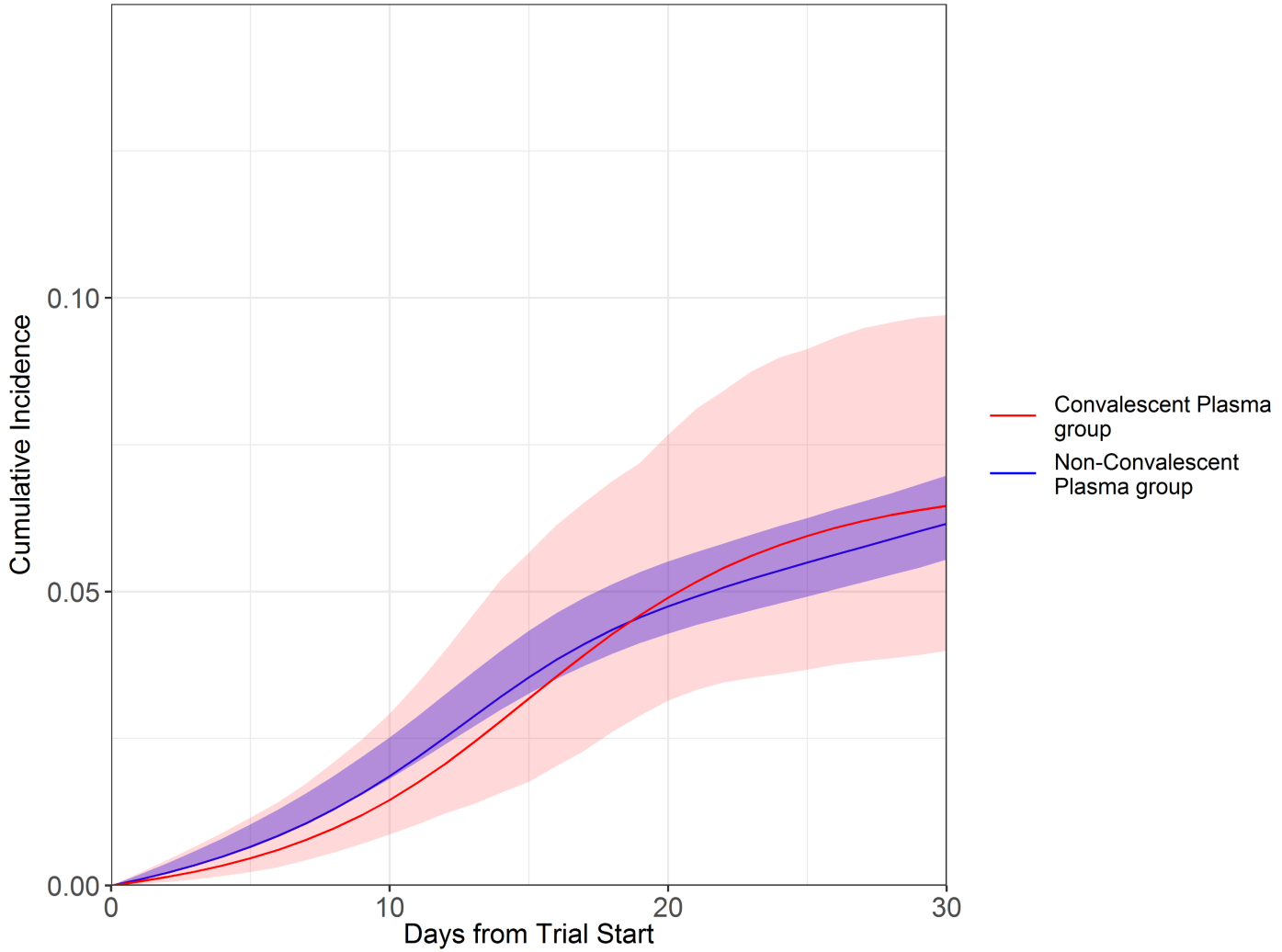
[§] During COVID-hospitalization prior to trial start



Love plot of standardized mean differences

*Vertical dotted line at 0.10, which is a common threshold for assessing balance of confounders after weighting.

Estimated cumulative incidence of 30-day mortality (with 95% confidence intervals)



30-day Risk Estimates

Convalescent Plasma:
6.5% (95% CI: 4.0, 9.7)

Non-Convalescent Plasma:
6.2% (95% CI: 5.6, 7.0)

30-day Risk Difference

0.30% (-2.30, 3.60)

30-day Hazard Ratio

1.04 (95% CI: 0.64, 1.62)

Discussion

- Our findings are compatible with those of the RECOVERY trial, the largest trial randomized trial of COVID-19 convalescent plasma (results were reported after our study was completed)
- Results from many observational studies may not be directly comparable to ours due to differences in causal questions and potential biases
- Strengths:
  - Largest observational study
  - Access to vast EMR data
  - Explicit specification of the target trial protocol components
- Limitation: No plasma titer data

Conclusions

- Our analyses do not support the use of convalescent plasma therapy in reducing mortality among non-severe COVID-19 patients
- Further research is warranted to assess the effect of convalescent plasma on progression to severe disease and the effective plasma dosing

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Appendix

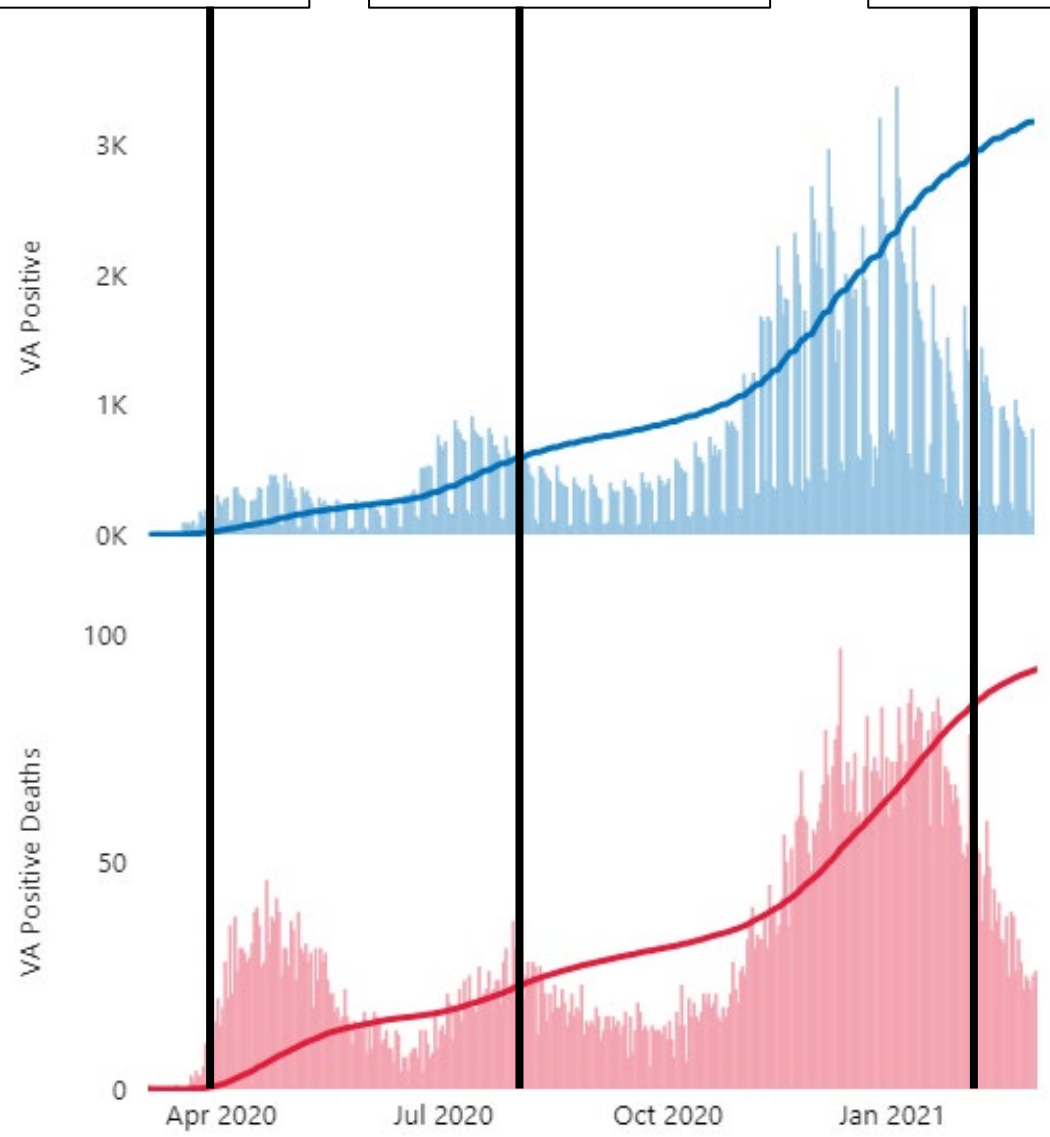
April 2020: Expanded Access Program (led by Mayo Clinic)

August 2020: FDA Emergency Use Authorization

February 2021: FDA Emergency Use Authorization Update

SARS-CoV-2 positive cases in VA

SARS-CoV-2 positive deaths in VA



Data from Veterans Affairs National Surveillance Tool