Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2103784

Early Administration of High Titer Convalescent Plasma in Emergency Department Patients with Mild/Moderate Covid-19 Illness.

The Clinical-trial of Covid-19 Convalescent Plasma in Outpatients (C3PO)

Supplementary Appendix - Table of Contents

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Inclusion / Exclusion Criteria over Time

All patients were enrolled under Protocol Versions 2, 3 or 4.

Version 2 - Recognized that knowledge about risk factors for progression to severe COVID-19 was evolving. Set CDC-defined risk factors as criteria in order not to exclude important subgroups (e.g. Sickle cell disease and obesity). Clarified that volume of placebo or plasma was <250 ml

Version 3 - Removed "mild" from description of population, because this word had developed specific meaning by that time that might exclude patients in emergency departments.

Version 4 - Clarified that the trial was to be conducted in patients with their first episode of COVID-19 after sites reported screening patients with recurrent COVID-19.

Version 5 - Clarified that randomization had to occur within 7 days of symptom onset. Exclude immunized persons, because both monoclonal antibodies and vaccines had become widely available.

Protocol Version 1 June 17, 2020	**Protocol Version 2 July 2, 2020**	**Protocol Version 3 September 7, 2020**	**Version 4 November 3, 2020**	**Version 5 February 16, 2021**
Adults presenting to the emergency department (ED) with **mild**, symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.	Adults presenting to the emergency department (ED) with **mild**, symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.	Adults presenting to the emergency department (ED) with symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.	Adults presenting to the emergency department (ED) with their **first episode** of symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.	Adults presenting to the emergency department (ED) with their first episode of symptomatic, laboratory-confirmed COVID-19 illness, who are at high risk for progression to severe/critical illness, but who are clinically stable for outpatient management at randomization.
Inclusion Criteria				
One or more symptoms of COVID-19 illness Laboratory-confirmed SARS-CoV-2 infection Has at least one study defined risk factor for severe COVID-19 illness: Age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney disease immunosuppression	One or more symptoms of COVID-19 illness Laboratory-confirmed SARS-CoV-2 infection Has at least one study defined risk factor for severe COVID-19 illness: **Study defined risk factors initially include:** age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney	One or more symptoms of COVID-19 illness Laboratory-confirmed SARS-CoV-2 infection Has at least one study defined risk factor for severe COVID-19 illness: Study defined risk factors initially include: age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney	One or more symptoms of COVID-19 illness Laboratory-confirmed SARS-CoV-2 infection Has at least one study defined risk factor for severe COVID-19 illness: Study defined risk factors initially include: age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney	One or more symptoms of COVID-19 illness Laboratory-confirmed SARS-CoV-2 infection Has at least one study defined risk factor for severe COVID-19 illness: Study defined risk factors initially include: age≥50 years; hypertension; diabetes; coronary artery disease; chronic lung disease; chronic kidney

Clinical team deems stable for outpatient management without supplemental oxygen ABO-compatible CP available at the site at the time of enrollment Duration of symptoms ≤ 7 days at ED presentation Signed informed consent	disease; immunosuppression; **sickle cell disease**, and **obesity (body mass index [BMI]>30)** and are **updated as needed in the C3PO Manual of Procedures in response to changes in CDC guidance or other information.** Clinical team deems stable for outpatient management without supplemental oxygen ABO-compatible CP available at the site at the time of enrollment Duration of symptoms ≤ 7 days at ED presentation Signed informed consent	disease; immunosuppression; sickle cell disease, and obesity (body mass index **[BMI]≥30)** and are updated as needed in the C3PO Manual of Procedures in response to changes in CDC guidance or other information. Clinical team deems stable for outpatient management without supplemental oxygen ABO-compatible CP available at the site at the time of enrollment Duration of symptoms ≤ 7 days at ED presentation Signed informed consent	disease; immunosuppression; sickle cell disease, and obesity (body mass index [BMI]≥30) and are updated as needed in the C3PO Manual of Procedures in response to changes in CDC guidance or other information. Clinical team deems stable for outpatient management without supplemental oxygen ABO-compatible CP available at the site at the time of enrollment Duration of symptoms ≤ 7 days at ED presentation Signed informed consent	disease; immunosuppression; sickle cell disease, and obesity (body mass index [BMI]≥30) and are updated as needed in the C3PO Manual of Procedures in response to changes in CDC guidance or other information. Clinical team deems stable for outpatient management without **new** supplemental oxygen ABO-compatible CP available at the site at the time of enrollment Duration of symptoms ≤ 7 days at ED presentation **and randomization**. Signed informed consent
Exclusion Criteria				
Age less than 18 years Prisoner or ward of the state Presumed unable to complete follow-up assessments Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days Treating clinical team unwilling to administer 300 ml fluid Enrollment in another interventional trial for COVID-19 illness	Age less than 18 years Prisoner or ward of the state Presumed unable to complete follow-up assessments Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days Treating clinical team unwilling to administer up to **250 ml** fluid Enrollment in another interventional trial for COVID-19 illness	Age less than 18 years Prisoner or ward of the state Presumed unable to complete follow-up assessments Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days Treating clinical team unwilling to administer up to 250 ml fluid Enrollment in another interventional trial for COVID-19 illness	Age less than 18 years Prisoner or ward of the state Presumed unable to complete follow-up assessments Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days Treating clinical team unwilling to administer up to 250 ml fluid Enrollment in another interventional trial for COVID-19 illness	Age less than 18 years Prisoner or ward of the state Presumed unable to complete follow-up assessments Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days Treating clinical team unwilling to administer up to 250 ml fluid Enrollment in another interventional trial for COVID-19 illness **or receipt of other active or passive immunization against SARS-CoV2.**

CDC Defined Risk Factors for Severe COVID-19

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

July 30, 2020	September 11, 2020	October 6, 2020	December 29, 2020	February 22, 2021
Cancer	Cancer	Cancer	Cancer	Cancer
Chronic kidney disease	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease
COPD (chronic obstructive pulmonary disease)	COPD (chronic obstructive pulmonary disease)	COPD (chronic obstructive pulmonary disease)	COPD (chronic obstructive pulmonary disease)	COPD (chronic obstructive pulmonary disease)
			Down Syndrome	Down Syndrome
		Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies	Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies	Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
Immunocompromised state (weakened immune system) from solid organ transplant	Immunocompromised state (weakened immune system) from solid organ transplant	Immunocompromised state (weakened immune system) from solid organ transplant	Immunocompromised state (weakened immune system) from solid organ transplant	Immunocompromised state (weakened immune system) from solid organ transplant
Obesity (body mass index [BMI] of 30 or higher)	Obesity (body mass index [BMI] of 30 or higher)	Obesity (body mass index [BMI] of 30 kg/m2 or higher but < 40 kg/m2)	Obesity (body mass index [BMI] of 30 kg/m 2 or higher but < 40 kg/m2)	Obesity (body mass index [BMI] of 30 kg/m 2 or higher but < 40 kg/m2)
Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies	Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies			
		Severe Obesity (BMI ≥ 40 kg/m2)	Severe Obesity (BMI ≥ 40 kg/m2)	Severe Obesity (BMI ≥ 40 kg/m2)
			Pregnancy	Pregnancy
Sickle cell disease	Sickle cell disease	Sickle cell disease	Sickle cell disease	Sickle cell disease
		Smoking	Smoking	Smoking
Type 2 diabetes mellitus	Type 2 diabetes mellitus	Type 2 diabetes mellitus	Type 2 diabetes mellitus	Type 2 diabetes mellitus

Ordinal Scales for Covid-19 Illness Severity

We quantified the worst illness severity during the 30 days after enrollment using the 8-category COVID Ordinal Scale for Clinical Improvement, as described in the World Health Organization (WHO) COVID-19 Trial Design Draft Master Protocol posted in February 2020. A score of zero, which would correspond to being virus-free, is not possible because we enrolled only patients with confirmed SARS-CoV2 infection.

WHO's COVID Ordinal Scale for Clinical Improvement

- 1 = Not hospitalized without limitation in activity (or limitations with no symptoms)
- 2 = Not hospitalized with limitation in activity (continued symptoms)
- 3 = Hospitalized not on supplemental oxygen
- 4 = Hospitalized on supplemental oxygen by mask or nasal prongs
- 5 = Hospitalized on non-invasive ventilation or high flow nasal cannula
- 6 = Hospitalized, intubated and mechanically ventilated
- 7 = Hospitalized, intubated, mechanically ventilated and requiring additional organ support (pressors, renal replacement therapy)
- 8 = Death

https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

This scale could be calculated from clinical information, but it differs from the 10-level WHO Clinical Progression Scale published in August 2020 after this trial was designed and initiated. (WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192–7).

We used an adaptation of the WHO Ordinal scale, based on the quality of symptoms reported by the subject, to quantify outpatient disease severity among patients at home (scores 1-2 on the WHO scale). This 5-level COVID Outpatient Ordinal Outcomes scale was adapted for outpatient use based on the work of Harrell 2020 (http://hbiostat.org/proj/covid19/bayesplan.html). This scale is hierarchical where 1 is the highest severity (hospitalization) and 5 is the lowest severity.

COVID Outpatient Ordinal Outcomes Scale

- 1 = patient requires care in the hospital
- 2 = patient requires care in the ED or urgent care
- 3 = patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain)
- 4 = patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath)
- 5 = patient in their usual state of health

Worsening of symptoms was defined as any subject admitted to the hospital (level 1), seen in the emergency room (level 2), a patient who reports increased symptoms of 2 levels on the scale over a 24-hour period, or a patient who reports increased symptoms of 1 level over a 48 hour period.

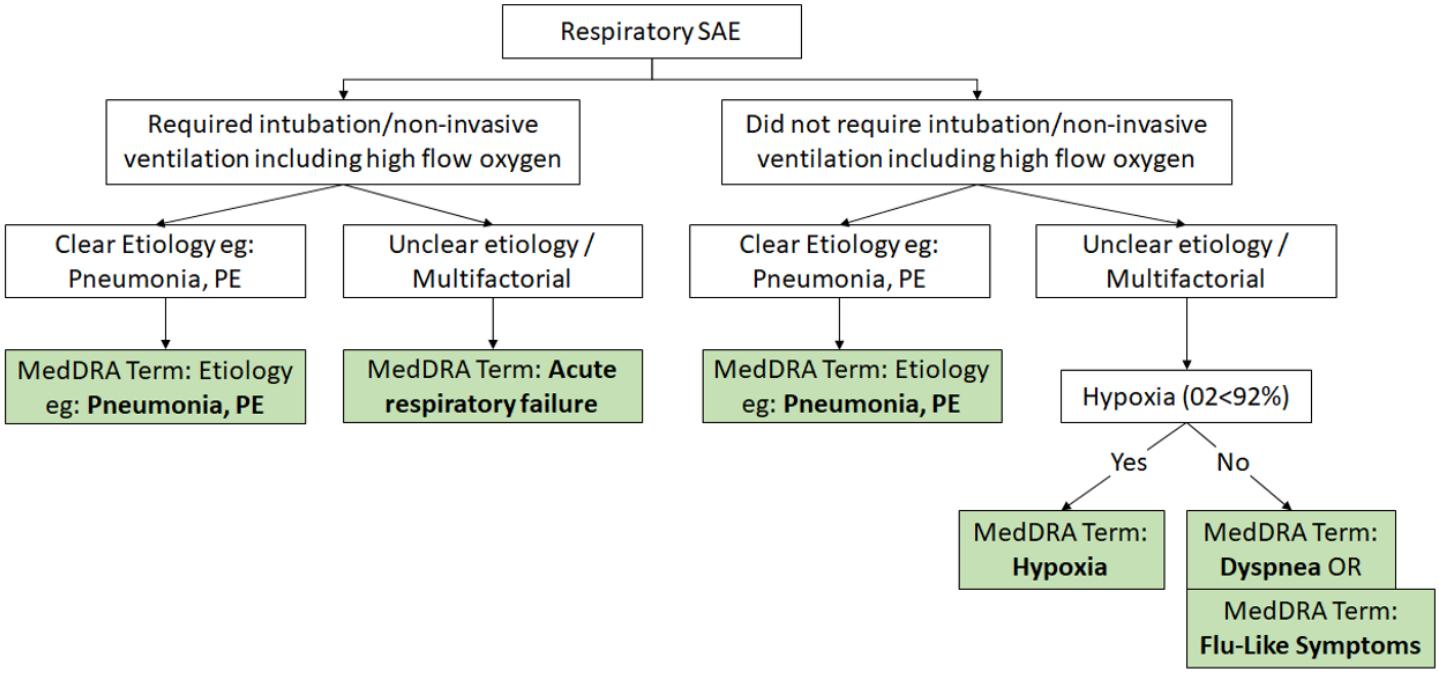
Multiple similar terms might be selected for reporting the progression of respiratory symptoms. To promote consistency, the enrolling sites were encouraged to use this guidance for selecting between these terms.

ACUTE RESPIRATORY FAILURE: This term should be utilized for subjects who are either intubated for respiratory failure or receive high flow oxygen supplementation if the etiology of the respiratory failure is unclear or multifactorial. If the etiology is clear for example: Pneumonia, Pulmonary Embolism, etc, use that name instead. Previously, investigators have used the following different terms that are similar to acute respiratory failure: ACUTE RESPIRATORY DISTRESS SYNDROME, ACUTE RESPIRATORY INSUFFICIENCY, RESPIRATORY DISTRESS, HYPOXIC RESPIRATORY FAILURE

PNEUMONIA: This term should be utilized for subjects that have clinical evidence of pneumonia. Previously, investigators have used the following different terms that are similar to pneumonia: ACUTE PNEUMONIA, BILATERAL PNEUMONIA, PNEUMONIA, PNEUMONIA DUE TO OTHER VIRUS NOT ELSEWHERE CLASSIFIED, PNEUMONIA VIRAL, VIRAL PNEUMONIA..

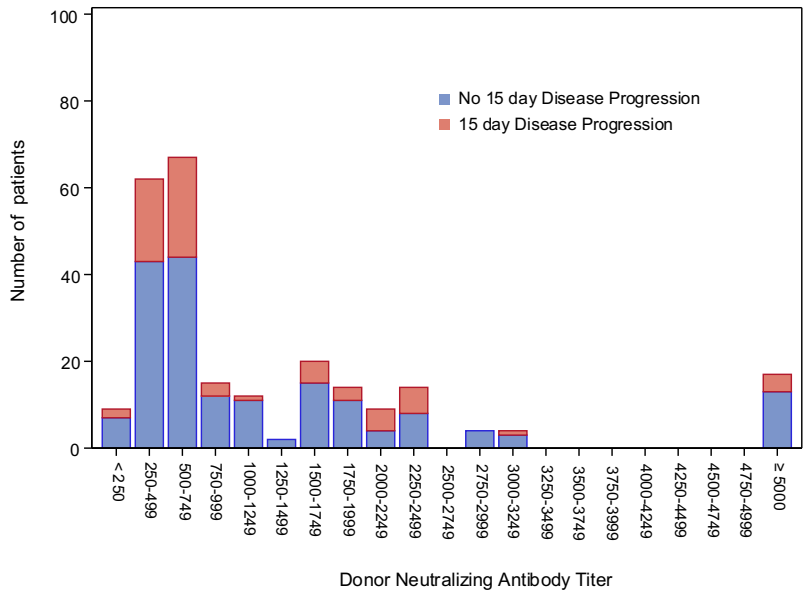
HYPOXIA: This term should be utilized for participants who have an oxygen saturation of <92% and no clear etiology for the hypoxia has been found. Previously, investigators have used the following different terms that are similar to hypoxia: HYPOXEMIA, HYPOXIA, OXIMETRY DECREASED, OXYGEN SATURATION DECREASED.

DYSPNEA: This term should be utilized for participants who have shortness of breath without a clear, more specific etiology and no hypoxia. Previously, investigators have used the following different terms that are similar to dyspnea: INCREASED SHORTNESS OF BREATH, SHORTNESS OF BREATH, SOB (SHORTNESS OF BREATH



Supplemental Tables and Figures

A. Distribution of Donor Titers and Patients with Disease Progression



B. Regression of Donor Titers to Probability of Disease Progression

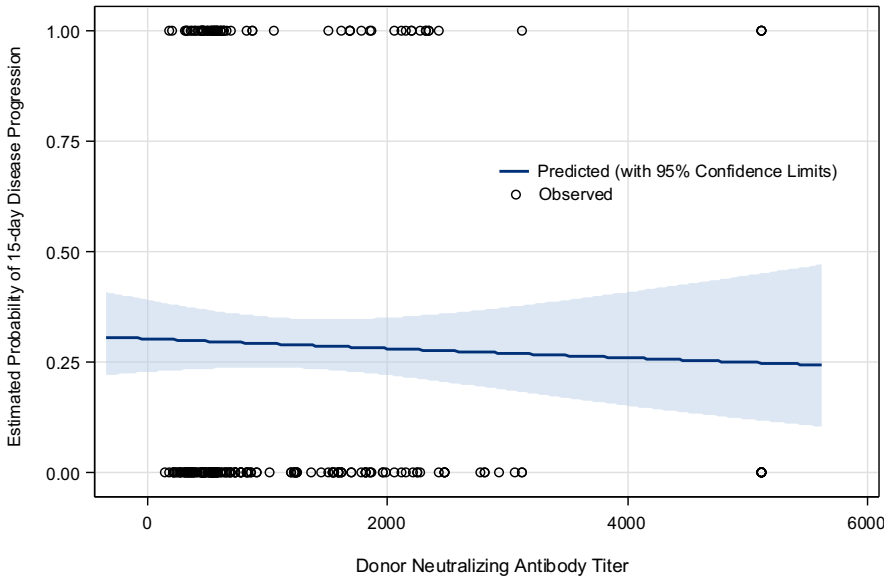


Figure S1. Distribution of donor CCP neutralizing antibody titers and association with disease progression

(A) Number of patients who received Covid-19 Convalescent Plasma (CCP) with donor neutralizing antibody titers within each specified range among patients with (red bars) or without (blue bars) progression of disease within 15 days of randomization. (B) Logistic regression model to examine the relationship between donor neutralizing antibody titers and the primary outcome of 15-day disease progression. The blue line indicates the predicted probability of disease progression (on the vertical axis) across the range of donor neutralizing antibody titers (on the horizontal axis), with the pale blue area indicating the 95% confidence limits. The small black circles indicate the observed data for each patient, either at 0.00 on the vertical axis (for those who did not have disease progression) or at 1.00 on the vertical axis (for those who did have disease progression). The probability of disease progression (y-axis) does not change as the titers (axis) increase, odds ratio (95% confidence interval): 1 (0.9997, 1.0002).

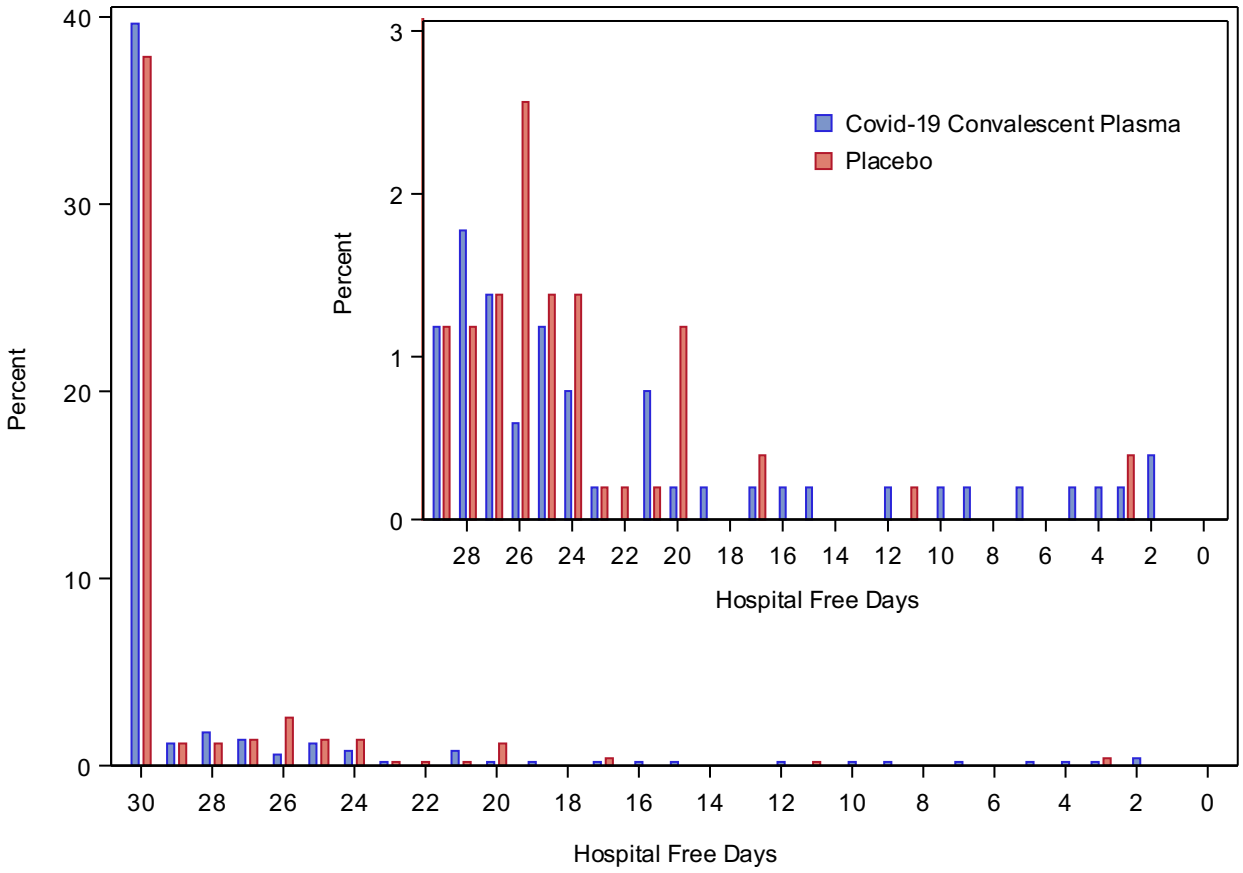


Figure S2. Secondary Efficacy Outcome - Hospital Free Days by Treatment Group

Distribution by treatment group of the number of hospital-free days among living patients within the 30-day study period. Inset shows a detailed view of distribution of hospital free days without the 30 hospital free days bar. Blue bars indicate percent of patients among those allocated to Covid-19 Convalescent Plasma. Red bars indicate patients allocated to placebo.

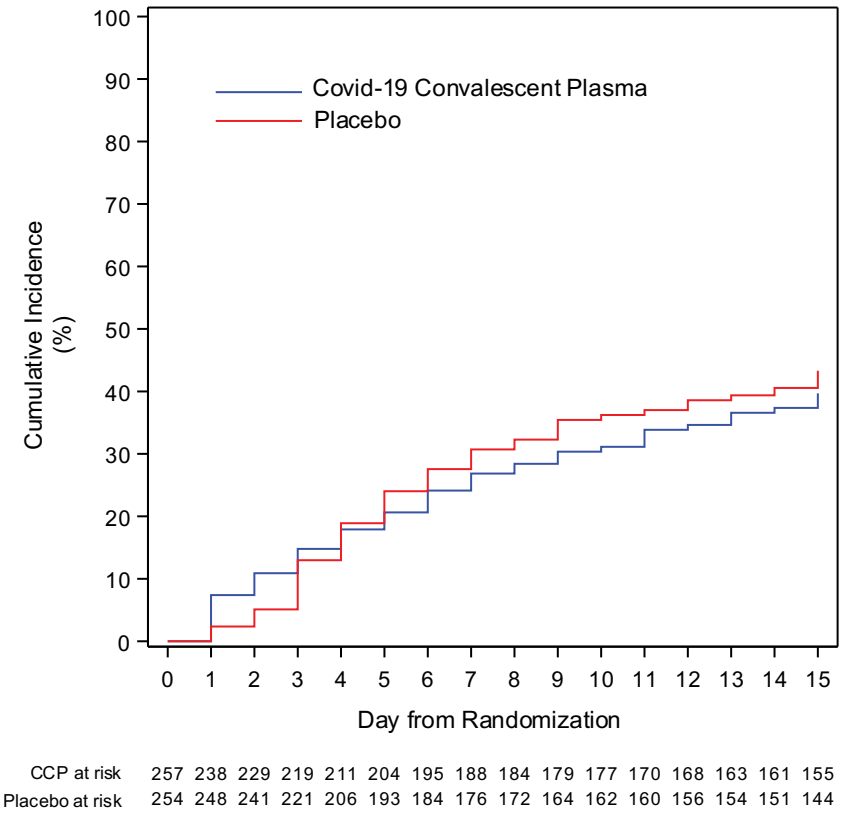


Figure S3. Secondary Efficacy Outcome - Time to Worsening of Symptoms

Cumulative incidence of symptom worsening within 15-days after randomization. Symptom worsening was defined using the 5-category ordinal scale or return for medical care. The blue line indicates CCP, and the red line indicates placebo. CCP = Covid-19 convalescent plasma.

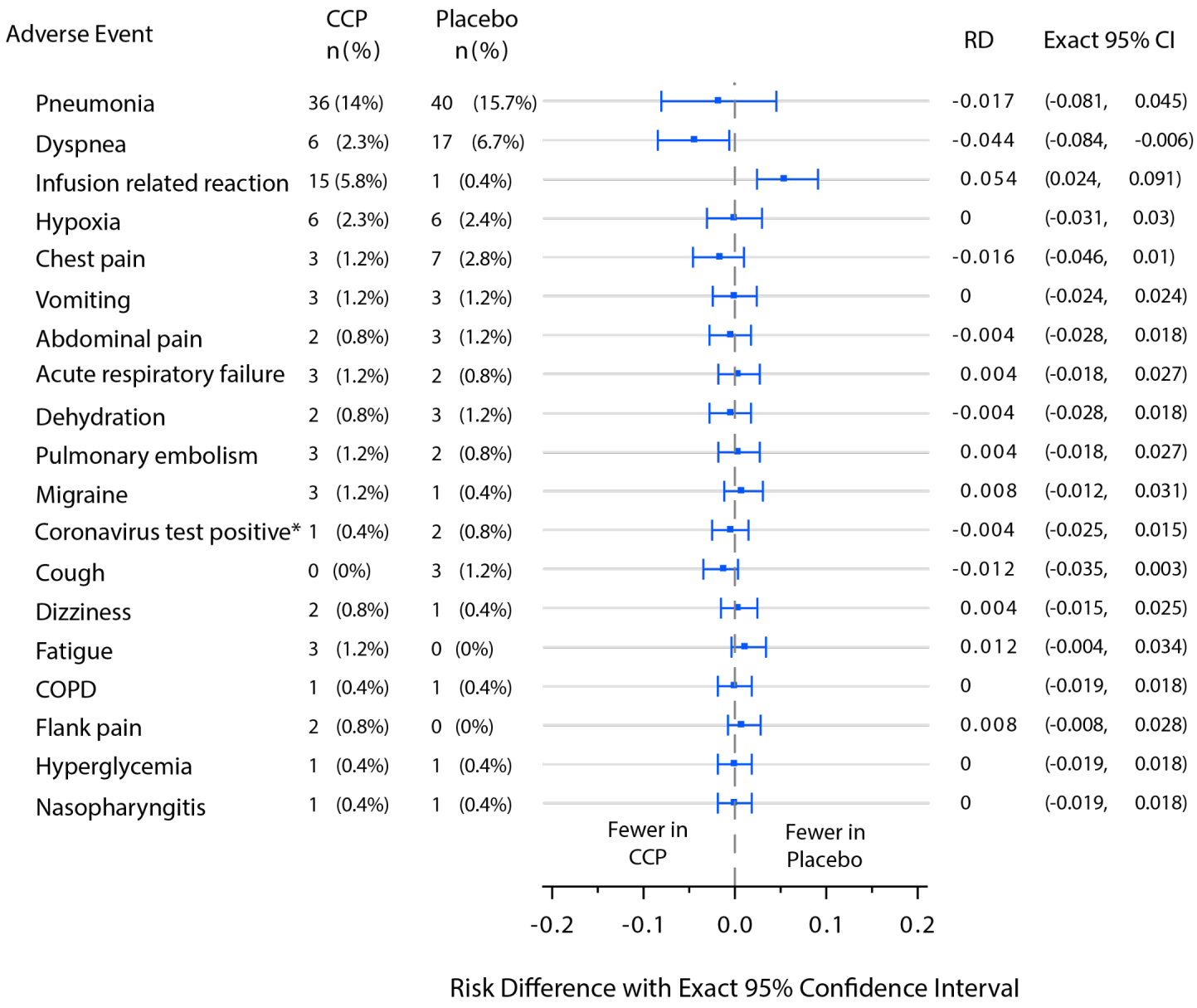


Figure S4. Adverse events, both serious and non-serious, occurring in ≥2 subjects - by treatment group

All adverse events, both serious and non-serious, occurring in 2 or more subjects listed by MedDRA preferred term or grouped similar preferred terms. Sixteen adverse events classified as "infusion related reactions" were definitely or possibly related to the study intervention. No other adverse events were classified as related to study intervention.

* "Coronavirus test positive" refers to patients who had a repeat visit to the emergency department post randomization for coronavirus testing (for example as a prerequisite for returning to work).

CCP = Covid-19 convalescent plasma, RD = Risk difference, CI = Confidence interval, COPD = Chronic obstructive pulmonary disease

Table S1. Source of CCP Donations

Region	Number of donors	Dates of donation
Chicago	140	6/27/2020 - 8/8/2020
Denver	98	7/27/2020 - 8/31/2020
Phoenix	4	9/18/2020 - 10/7/2020
PIttsburgh	7	5/7/2020 - 6/8/2002

Table S2. Post-hoc Sensitivity Analyses Investigating 25 Patients Admitted During the Index Visit

	Covid-19 Convalescent Plasma	Placebo
Sensitivity analysis		
Intention to treat population, n	257	254
Patients Admitted During the Index Visit, n (%)	19 (7%)	6 (2%)
Primary outcome after exclusion, n (%)	58 (24%)	75 (30%)
Risk difference after exclusion, risk difference (credible interval)	5.8% (-1.9% to 13.6%)	
Posterior Probability that CCP was superior	0.93	
Per protocol population (n)	246	251
Patients Admitted During the Index Visit,n (%)	16 (7%)	6 (2%)
Primary outcome after exclusion, n (%)	55 (24%)	74 (30%)
Risk difference after exclusion, risk difference (credible interval)	6.2% (-1.7% to 14.1%)	
Posterior Probability that CCP was superior	0.94	
Patient characteristics of those admitted during the index visit		
Reason for early admission		
Pneumonia or hypoxia, n	12	4
Infusion related reaction, n	3	0
Other. N	4	2
Infusion never initiated, n	2	0
Randomization to infusion start - median minutes (IQR)	113 (89 to 154)	24 (23 to 94)
Hospital length of stay - median days (IQR)	4 (2 to 6)	5 (3 to 8)

IQR = interquartile range

Table S3. Characteristics of 6 Patients Who Died Within 30 Days from Randomization

Age yr	**Gender**	**Treatment Group**	**Eligibility Risk Factors** n	**Name of Fatal Adverse Event**	**Time interval** - days		
					Symptom Duration Prior to Randomization	**Randomization to Disease Progression**	**Randomization to Death**
72	Male	CCP	2	Pneumonia	3	2	27
49	Female	CCP	3	Pulmonary embolism	6	7	7
55	Female	CCP	4	Acute respiratory failure	2	10	10
55	Male	CCP	7	Pneumonia	6	0	23
75	Female	CCP	5	Hypoxia	3	1	17
87	Male	Placebo	2	Pneumonia	1	3	5

No deaths were classified as related to study intervention. Adverse events represent the name assigned to the event at its onset.

CCP = Covid-19 Convalescent Plasma
yr = years

Table S4. Adverse events, both serious and non-serious, occurring in only 1 subject listed by treatment group, n=1 (0.4%)

MedDRA Preferred Terms

Covid-19 Convalescent Plasma	Placebo
Acute kidney injury	Anemia
Alcohol poisoning	Decreased appetite
Anaphylactic reaction	End stage renal disease*
Anxiety	Esophagoscopy
Asthma	Hemoptysis
Atrial fibrillation	Hyperkalemia
Bronchospasm	Hyponatremia
Depression	Iliac artery occlusion
Dysphagia	Influenza like illness
Ecchymosis	Paranoia
Epilepsy	Presyncope
Epistaxis	Psychotic disorder
Fall	Septic shock
Hypotension	Tachycardia
Infusion site extravasation	Thrombophlebitis superficial
Nephrolithiasis	Venous thrombosis limb
Pyrexia	
Rash	
Road traffic accident	
Sinusitis	
Tooth abscess	
Tooth extraction	
Vertigo	
Viral diarrhea	

* Patient with end-stage renal disease could not receive hemodialysis as an outpatient due to having Covid-19 and was admitted for dialysis.